SOCIEDAD MEXICANA DE ONCOLOGÍA, A.C.

# GACETA MEXICANA DE ONCOLOGÍA

VOLUME 16, NÚM. 1, JANUARY-FEBRUARY 2017

ISSN: 1665-9201

INDEXADA EN SCOPUS • ARTEMISA • LILACS • IMBIOMED • PERIODICA-UNAM

# **EDITORIAL**

The Mexican Gazette of Oncology (GAMO) Evolves in its Publication

Genetics as a Tool in Oncology Daily Practice

#### **ORIGINAL ARTICLES**

Use of Ipilimumab in Patients Diagnosed with Metastatic Melanoma: Three-Year Experience in a Private Hospital in Mexico City

Latissimus Dorsi Myocutaneous Extended Flap in the Reconstruction of Large Chest Wall Defects after Extensive Resections in Breast Pathology

Prognostic Factors in Patients Diagnosed with High Grade Glioma Managed with Radiotherapy: Experience at the Federico Gómez Children's Hospital of Mexico

Cost-Benefit Study of Febrile Neutropenia Prophylactic Treatment with Pegfilgrastim vs. Filgrastim in Pediatric Patients with Solid Tumors

Clinical Genetics: Basic Concepts for Oncology Practice

#### **REVIEW ARTICLES**

Radiotracers Used in Nuclear Medicine for Prostate Cancer Diagnosis and Follow-Up

Can Omega 3 Supplements Prevent Cancer Therapy Neurocognitive Toxicity?

Health Economic Assessment: Applications, Rationale, Methodology and Common Mistakes

#### **CLINICAL CASE**

Paratesticular Desmoplastic Tumor: Case Report and Review of Literature

Medullary Thyroid Cancer Metastatic to the Oral Cavity: Clinical Case

Treatment with Radium 223 in a Patient with Castration-Resistant Metastatic Prostate Cancer: A Case Report

Incidentally-Diagnosed Multiple Endocrine Neoplasia IIA (Sipple Syndrome) with Bilateral Pheochromocytoma and Medullary Thyroid Carcinoma





www.smeo.org.mx www.elsevier.es/gamo



# EDITORIAL

SOCIEDAD MEXICANA DE ONCOLOGÍA, A.C. GACETA MEXICANA DE ONCOLOGÍA WWW.gamo-smeo.com



# The Mexican Gazette of Oncology (GAMO) Evolves in its Publication

Samuel Rivera-Rivera<sup>1</sup> and Francisco Javier Ochoa-Carrillo<sup>2,\*</sup>

<sup>1</sup>Chairman, Sociedad Mexicana de Oncología (SMeO), <sup>2</sup>Editor in Chief, Gaceta Mexicana de Oncología (GAMO), Mexico City, Mexico

As the official scientific dissemination journal of the Mexican Society of Oncology (SMeO - Sociedad Mexicana de Oncología), the Mexican Gazette of Oncology (GAMO - Gaceta Mexicana de Oncología) has achieved 14 years of existence, hitherto being able to maintain both bimonthly periodicity and continuity in Spanish, meeting the international standards of professional scientific publications, with a selection of peer-reviewed articles, and enriched by contributions coming from Latin America, the USA, and Europe. In addition, our journal has maintained an impeccable editorial presentation with color images, high-definition printing, and high-quality paper, with significant indexing, open for free access on the internet, but especially being increasingly consulted in different parts of the world through different international bibliographic databases and with the support of a renowned publishing house such as Elsevier.

Development always brings about changes, which is nothing but the result of an evolutionary process that generates new phenomena, such as the transition from the printed to the electronic format, or as once occurred with the transition from handwritten to printed texts. This elicits a change in production, dissemination and information authentication processes, and all stakeholders involved with these processes (authors, editors, information professionals, etc., all in their roles as information providers) have therefore been compelled to open spaces to these new electronic versions, with this being the case of the GAMO.

On the other hand, one of the most notorious characteristics of medical writing in the last third of the 20<sup>th</sup> century, and so far in the 21<sup>st</sup>, is the predominance of English as the only international language of medicine.

Among the repercussions the boom of English language has had on medicine over the past few decades, which have driven to its current situation of absolute predominance in scientific communication, physicians will mainly cite two: the influence of English on current medical language and the simplification of international communication. Nevertheless, the fact that the influence of the English language is more widespread and intense, and that it affects all levels of language in orthographic, lexical, and syntactic aspects, seems to be often forgotten.

The appearance of Medline, which brought literature search automation, has allowed for it to be amazingly simplified, but has also led scientists to restrict their searches to the last 35 years (Medline only covers the period from 1966 to the present day) and to automatically eliminate articles published in other languages, thanks to the possibility to conduct automatic searches with the "English only" restriction criterion<sup>1</sup>.

Furthermore, since large bibliographic databases preferably incorporate journals in English, articles published in large Anglo-North American medical journals barely contain references to publications in other languages.

Another fact that drives this eagerness of researchers to publish in English and, if possible, in journals with international circulation, is that the editorial boards of these journals, as well as the scientific committees of the main international congresses, are mainly comprised by Anglo-North American scientists.

The famous English saying "publish or perish" has thus become, in Spanish-speaking countries, the bilingual disjunctive "publica o muere"; i.e., for Spanish language scientists, the fact comes down now to a situation of whether "to be or not to be" in the international medical community<sup>2</sup>.

The SMeO, within its growth and evolution, aware of this reality, and in an effort to make the presence of researchers who collaborate with the GAMO more visible, in addition to continuing to publish the journal in Spanish, is now simulta-

http://dx.doi.org/10.24875/j.gamo.17000014

<sup>\*</sup>E-mail for correspondence: ochoacarrillo@prodigy.net.mx (F.J. Ochoa-Carrillo)

<sup>1665-9201 / © 2017</sup> Sociedad Mexicana de Oncología. Publicado por Permanyer México. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

neously releasing, from this issue onwards, the full-English version. This unprecedented effort, after several years of fruitless attempts, is now a reality, and we inform that the printed paper version will disappear, with the journal being electronically available in both languages (Spanish and English).

Currently, new scientific and technological advances require rapid dissemination to the benefit of specific necessities. Electronic publishing has turned out to be an efficient vehicle for the dissemination of contents, since it is one of the scientific communities' main means of communication, which facilitates exchange between peers from different geographic locations.

Electronic publishing requires increasingly more efficient means of communication, and demands better skills for consultation as well. The Internet favored the evolution of electronic publishing as telecommunication networks were developing; sometimes, other technologies allowed for coverage to be broadened, as in the case of CD-ROMs, which came to be a means of electronic distribution par excellence prior to the advent of the internet.

As it was consolidating, electronic publishing saw the emergence of a variety of information resources (e-journals, e-books, e-bulletins, among others), and academic communities began to be assiduous users of such resources.

# ADVANTAGES AND DISADVANTAGES OF THE E-JOURNAL<sup>3</sup>

The conformation of the e-journal is strongly associated with the publication's information architecture, and hence interaction with the document is more or less possible. Nevertheless, as such, the electronic publication has the following advantages:

- It preserves rare and fragile documents, without restricting access to those who wish to consult them.
- It facilitates transmission by means of telematic networks.
- It enables simultaneous access to many users.
- It offers a solution to the problem of physical space for storage.
- It reduces publishing and distribution costs by using electronic means for the transmission of information.
- It enables full-text searches.
- It facilitates instantaneous access without the need to go elsewhere.
- It provides links to other related resources, such as filmed and animation materials, which facilitates the expression of ideas that are difficult to capture in a printed format.
- It establishes a close relationship between authors and readers through e-mail, which favors scientific communication.
- It allows immediate publishing, based on a system of continuous production.
- It enables incorporating corrections or comments made by readers.
- It reduces paper consumption costs since printed copies are made only for articles that are really of interest, thus favoring ecology.

In addition to the above points, we can add further characteristics that new technologies contribute within electronic devices, such as smartphones or PDAs, where the complete collection of one or several titles can be stored.

The nature of e-publishing eliminates many of the steps related to print publishing in the relationship between publishers/providers and the libraries: printing, binding, packaging, distribution, transportation, postal fees and storage costs.

As well as the observed advantages, there are also some disadvantages:

- Considerable initial investment, although e-journals are more economical in the long-term.
- On-screen visualization inconvenience, although the PDF file format is an advance in this sense.
- High costs of publication subscriptions.
- A language barrier in our countries since the resources are mainly in English language.
- Internet connection is required, with additional costs with regard to telecommunication infrastructure.

In light of the attitude of commercial publishers in the market of information, other initiatives have started to emerge, including the "Open Access" initiative. Given its impact, considering a series of definitions on the subject is suggested: The Open Access (OA) initiative represents a new academic publishing model, developed for free investigators and libraries; it emerged as a reaction to limitations imposed by excessive increases in subscriptions to peer-reviewed journals, especially in the fields of science and medicine. By breaking the publishers' monopoly on scientific research distribution, Open Access enables more equitable access to information, with the additional advantage that it allows for authors to keep the copyright of their works.

Open Access Journal: This is a periodical scholarly publication that offers full-text articles that are freely and universally published on the Internet, by immediately and with no restriction whatsoever depositing them in a widely recognized, open access repository, as in the case of GAMO.

The impact factor of a journal is the mean number of times an article published in a particular journal is cited. It is an instrument to compare journals and to assess the relative importance of a journal within a specific scientific field. Thomson ISI is in charge of analyzing journals for this purpose, and this project is therefore intended to consolidate this aspect.

As of this issue, we have also made some changes in the editorial board, enriching it with prominent national and international opinion leaders that, with their editorial experience, will surely contribute to improving article selection since, fortunately, we receive high-quality manuscripts and in a considerable number, which provides the opportunity to select.

And so it was that, at this new stage, the SMeO has established an agreement with Permanyer, which is a medical publishing house founded in Barcelona in 1973.

Currently, it has offices in Spain, Switzerland, Mexico, Brazil, and Portugal and commercial presence in more than 25 countries.

Permanyer is specialized in periodical peer-reviewed medical publications, and has systems and channels of its

own for publishing in English and Spanish, among other languages, as well as for subsequent electronic dissemination and content indexing in the main global indexing systems, such as, for example, PubMed, Medline, and Thomson Reuters, among others.

Manuscript handling is carried out by means of an electronic process with personalized software offered by the publishing house, where authors submit their manuscripts for review and the system connects Editors and Reviewers for articles to be followed-up until publication approval, thus enabling several reviews and updates of the same manuscript until its acceptance. Once approved by the editors, the publishing house carries out a review of the text under high-quality standards following the International Committee of Medical Journal Editors recommendations and publishes the articles for indexing, both in the printed and electronic forms, in the journal's website, which is provided by the publishing house.

It possesses the electronic infrastructure required to provide and maintain website functioning of scientific journals and has wide experience in scientific journal indexing in different international information recovery and bibliometric systems such as, for example, Thomson-Reuters, Medline/ PubMed, etc. In 2000, Permanyer obtained the ISO 9001 quality accreditation for scientific publication, and has renewed it every year by means of detailed audits as a sign of commitment to the final quality of its publications. This company has had a presence in Mexico since 2005 and, currently, it publishes reference journals that meet international quality standards for medical/scientific publications.

Dear reader, the SMeO and GAMO are working to evolve and to offer an attractive option for researchers and potential users and to be consulted in Spanish and/or English, and in this way provide a better service to the oncologic community of Mexico and all over the world.

# REFERENCES

- Jennings AG. Research or re-search? Why we should read old and foreign literature. Ann R Coll Surg Eng. 1994;76(5 Suppl):236-7.
- Ren S, Liang P, Zu G. The challenge for Chinese scientific journals. Science. 1999;286(5445):1683.
- Travieso Aguiar M. Las publicaciones electrónicas: una revolución en el siglo XXI. Acimed. Marzo-abril de 2003. Vol. 11, n.o 2. [Internet] Disponible en: http://www.bvs.sld.cu/revistas/aci/vol11\_2\_03/aci010203.
- Reitz JM. ODLIS: Online Dictionary for Library and Information Science. Wesport, Washington: Libraries Unlimited. Disponible en: http://www. abc-clio.com/ODLIS/odlis\_A.aspx.



SOCIEDAD MEXICANA DE ONCOLOGÍA, A.C. GACETA MEXICANA DE ONCOLOGÍA www.gamo-smeo.com



# Genetics as a Tool in Oncology Daily Practice

# Herber García-Castillo<sup>1,\*</sup> and Francisco Javier Ochoa-Carrillo<sup>2</sup>

<sup>1</sup>Life in Genomics, <sup>2</sup>Department of Surgical Oncology, Instituto Nacional de Cancerología and Hospital Ángeles del Pedregal; Mexico City, Mexico

Received for publication: 11 December 2016; accepted for publication: 25 February 2017 Available online: 10 July 2017

The oncology consultation is enriched by genetics. This new science is revolutionizing oncological clinical practice. It contributes with elements to understand the pathophysiology of cancer, and enables comprehensive diagnosis and patient management from the knowledge of new therapeutic targets, passing through hereditary cancer and new clinical diagnoses integration, and up to the prognosis and treatment of sporadic cancers.

Currently, there are a wide variety of genetic studies and tools available: tests for hereditary cancer, expression studies for the prediction of metastasis, pharmacogenetics, microarrays, comparative genomic hybridization, etc. But, what do these studies consist in? When should they be ordered? Which patients are candidates? Is it better to request individual studies or gene panels? What requirements should the laboratories that perform these tests meet? In what cases should consultation with the genetics department be requested? The oncologist asks him/herself these and other questions when faced with the decision to prescribe a genetic study.

However, these questions are not that easy to answer since many of them require knowledge on the basic concepts of clinical genetics and on the specific areas where the knowledge is applied.

In view of the above, in this issue we will start with a series of bimonthly articles intended to update oncologists on the application of genetics to oncological clinical practice. We will start with an article appearing in this issue entitled "Clinical genetics: Basic concepts for oncology practice". As with any other specialty, clinical genetics uses its own terminology and some of it can be foreign to the oncologist. This article gives an introduction to this world in simple language and with educational examples for better understanding.

PERMANYER

In future issues we will further address subjects such as: genetic counseling, genetic alterations in cancer, biomarkers in oncology, international recommendations for the use of genetic tests in oncology practice, hereditary cancer syndromes, genes vs. panels, pharmacogenetics, gene expression tests, assessment and risk management in hereditary breast and colon cancer, prophylactic surgery and surgical approaches based on molecular studies, cost-effectiveness in the management of hereditary cancer, the patient's point of view, and the hereditary cancer management approach by interdisciplinary teams.

There are several examples of the usefulness of genetics in oncological practice, since over the last years, medications used in oncology have changed, based on the knowledge of molecular pathways and biomarkers (specific molecules that are over-expressed in cancer)<sup>1</sup>, which are of great value in the prediction of response to therapy and have acquired relevance in oncological daily practice, such as the use of HER2 or EGFR, to the benefit of a large subgroup of patients over the past few years (Table 1).

Currently, there are more than 50 oncologic drugs with FDA-approved genetic biomarker information included in the summaries of product characteristics or patient information leaflets. This list includes some drugs that are specially prescribed when there is some genetic alteration, as in the case of the treatment of non-small cell lung cancer with afatinib,

http://dx.doi.org/10.24875/j.gamo.17000001

<sup>\*</sup>E-mail for correspondence: herbertgarcia@lifeingenomics.com (H. García-Castillo)

<sup>1665-9201 / © 2017</sup> Sociedad Mexicana de Oncología. Publicado por Permanyer México. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Table 1.         Commonly use	d biomarkers in oncolog	у		
FDA Approval	Cancer	Benefited patients	Drug	Biomarker
Nov, 2004	Lung CA	15%	Erlotinib	EGFR
April, 2003	Chronic myeloid leukemia	95%	Imatinib	BCR-ABL
Sept, 1998	Breast CA	15-20%	Trastuzumab	HER2

CA: cancer; FDA: Food and Drug Administration.

Table 2. US Food and Drug Administration-approved drugs indication or contraindication according to the presence of mutations

Drug	Type of cancer	Gene	Mutation	Implication
Afatinib Erlotinib Gefitinib Osimertinib	Metastatic non-small cell lung cancer	EGFR	Exon 19 and 21 deletion (L858R) T790M	Indication
Cobimetinib Dabrafenib Pembrolizumab Trametinib Vemurafenib	Metastatic melanoma	BRAF	V600E/K	Indication
Olaparib	Advanced ovarian cancer	BRCA1/2	Germline mutations (inherited)	Indication
Cetuximab Panitumumab	Metastatic colorectal cancer	KRAS	Exons 2, 3, 4 deletion (codons 12,13, 59, 61, 117, 147)	Contraindication

erlotinib, gefitinib, osimertinib; chemotherapy in metastatic melanoma with cobimetinib, dabrafenib, pembrolizumab, trametinib, and vemurafenib; and advanced ovarian cancer with olaparib. Conversely, some mutations are a contraindication for the prescription of certain drugs such as cetuximab and panitumumab<sup>2</sup> (Table 2).

The use of gene expression panels such as MammaPrint<sup>®</sup> and OncotypeDx<sup>®</sup> is increasingly common in patients with breast cancer at early stages with the purpose to discern which patients can benefit from adjuvant chemotherapy and which patients do not require it.

MammaPrint<sup>®</sup> is a 70-gene assay that uses microarray technology, requires frozen tissue, and is used in patients with stage I and II breast cancer with negative lymph nodes or 1-3 positive lymph nodes to identify those patients who may benefit from adjuvant chemotherapy based on high or low genomic risk for cancer distant recurrence and at five and 10 years. The MINDACT prospective trial, which is following a cohort of more than 6,000 patients, has found that patients with post-surgery clinical high risk and genomic low risk without chemotherapy have a five-year survival without distant metastasis of 94.7% (95% CI: 92.5-96.2)<sup>3</sup>.

On the other hand, OncotypeDx<sup>®</sup> is a 21-gene expression assay that includes *ER*, *PR*, *HER2* and *Ki67* in breast cancer for ER-positive, HER2-negative and lymph node-negative women. The technology used is reverse transcription polymerase chain reaction (RT-PCR), which requires paraffin-embedded tissue. Patients are classified according to a recurrence score to distinguish those who may benefit from adjuvant chemotherapy: patients with a 0-10 score are assigned to receive endocrine therapy, those with a score higher than 26 are given chemotherapy and endocrine therapy, and patients with 11 to 25 points remain in an unspecified group (since benefit of chemotherapy has not been defined for them). This expression profile is considered to be predictive of tamoxifen and adjuvant chemotherapy efficacy. The TAILORx prospective trial, carried out in over 10,000 patients, showed that 15.9% of patients belong to the 0-10 recurrence risk group, which received endocrine therapy alone and have a five-year invasive disease-free survival rate of 93.8% (95% CI: 92.4-94.9)<sup>4</sup>.

In addition to genetic studies as a tool in the prescription of chemotherapy, a very interesting field is the use of genetic testing in patients with hereditary cancer; between 5-10% of cancers are estimated to be hereditary, and their clinical management is different to that of sporadic cancer.

For example, in the breast and ovary cancer hereditary syndrome positive to BRCA mutation, where the risk for having breast cancer and/or ovarian cancer is as high as 41-90%, there is also an increased recurrence of contralateral breast cancer as high as 32% at 10 years and 44% at 70 years of age and, therefore, bilateral mastectomy is recommended in newly-diagnosed patients, and owing to a risk for ovarian cancer of up to 44% at 70 years of age, the risk-reduction salpingo-oophorectomy option is recommended after 35 years of age with satisfied parity. These procedures help to reduce the risk of breast and ovarian cancer by 95 and 90%, respectively<sup>5</sup>. It should be noted that some patients do not prefer the risk-reducing surgery option and, consequently, close surveillance with imaging studies and serum marker determination every six months is the option. The drug olaparib is currently available for patients

with advanced ovarian cancer positive to inherited mutation in the *BRCA* genes, and 3 poly(ADP-ribose) polymerase (PARP)-inhibitor drugs are in phase III studies for *BRCA*-positive breast cancer.

Clinical criteria in hereditary cancer are increasingly less rigorous as a primary screening method in order to include the largest number of patient candidates to genetic studies. In hereditary breast and ovarian cancer syndrome, the National Comprehensive Cancer Network (NCCN) criteria include, among others, patients with breast cancer younger than 45 years, ovarian cancer at any age, triple-negative breast cancer prior to 60 years of age, and two cancers of the spectrum ovarian, fallopian tube, prostate, pancreas or peritoneum in the family<sup>5</sup>.

There are studies available on high-penetrance genes such as BRCA; however, there are also panels of several genes containing up to 30 genes related to hereditary cancer, and the clinician should know the degree of penetrance of different genes in hereditary cancer, as well as the differential diagnoses to know if prescribing a genetic panel is convenient, since not all results are clinically applicable.

Genetics is a fascinating science and it is very promising for oncology. We illustrate some relevant applications of genetics in oncological daily practice, and in future issues we will complement the provided information. We will start in this issue with the bases of clinical genetics in the article entitled "Clinical genetics: Basic concepts for oncology practice"; we hope it will be of interest and serve as a contribution to a current clinical practice update.

# REFERENCES

- Ferté C, André F, Soria JC. Molecular circuits of solid tumors: prognostic and predictive tools for bedside use. Nat Rev Clin Oncol. 2010;7:367-80.
- US Food and Drug Administration. Table of Pharmacogenomic Biomarkers in Drug Labels. Available at: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm (Accessed Jan 15, 2017).
- Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med. 2016;375:717-29.
- Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med. 2015;373:2005-14.
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian, 2017. Available at: https://www.nccn.org/professionals/ physician\_gls/f\_guidelines.asp (Accessed Jan 15, 2017).



# SOCIEDAD MEXICANA DE ONCOLOGÍA, A.C. GACETA MEXICANA DE ONCOLOGÍA WWW.gamo-smeo.com



# ORIGINAL ARTICLE

# Use of Ipilimumab in Patients Diagnosed with Metastatic Melanoma: Three-Year Experience in a Private Hospital in Mexico City

Christian Patricio Camacho-Limas<sup>1,\*</sup>, Guillermo Olivares-Beltrán<sup>1</sup>, Raquel Gerson-Cwilich<sup>2</sup>, Alberto Villalobos-Prieto<sup>1</sup>, María del Ángel Góngora-Jurado<sup>3</sup> and Alain Sánchez-Rodríguez<sup>4</sup>

<sup>1</sup>Department of Medical Oncology, <sup>2</sup>Cancer Center, <sup>3</sup>Clinical Pathology, and <sup>4</sup>Internal Medicine; Centro Médico ABC, Mexico City, Mexico

Received for publication: 31 August 2016; accepted for publication: 25 February 2017 Available online: 10 July 2017

KEYWORDS

Melanoma; Ipilimumab; Immunotherapy Abstract Objective: Ipilimumab is an antibody for the treatment of metastatic melanoma that currently is scarcely accessible for most cancer centers in Mexico, and this is why a descriptive analysis was carried out in the ABC Hospital, with this being one of the few centers that use this drug in the entire country. Material and methods: A three-year observational study was carried out with the general purpose to describe the clinical course of ipilimumabtreated patients and with the specific purpose to perform an overall survival analysis. Demographic, diagnostic, therapeutic, and clinical variables were analyzed. The response was assessed according to Wolchok's immune response criteria. Results: Thirteen patients were included, out of which 53% (7/13) were females and 46% (6/13) males, with a median age of 54 years at diagnosis. Median total follow-up of the population was 18 months, and all patients were treated with ipilimumab 3 mg/kg every three weeks for four sessions. Overall survival and progression-free survival had a median of 18 (IQR: 8-24) and 5 (IQR: 4-24) months, respectively. Conclusions: In this cross-sectional cohort analysis, observations on metastatic or recurrent melanoma treatment with ipilimumab published up to now were corroborated. With a response rate of 23%, an essential outcome is a response duration of more than 28 months until current follow-up of the patients who show an objective response with the use of ipilimumab. (creativecommons.org/licenses/by-nc-nd/4.0/).

\*E-mail for correspondence: dr.camacholimas@gmail.com (C.P. Camacho-Limas)

http://dx.doi.org/10.24875/j.gamo.17000002

1665-9201 / © 2017 Sociedad Mexicana de Oncología. Publicado por Permanyer México. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

# INTRODUCTION

Melanoma accounts for 4% of all malignancies of the skin, although it is responsible for 80% of deaths associated with this type of neoplasm. Most melanomas are located in the skin (95%), and less frequently (5%) in mucous membranes (oral, gastrointestinal tract, genital), the retina, or meninges. Approximately 3% of patients develop occult melanomas (metastatic disease with no evidence of a primary tumor)<sup>1</sup>.

#### **EPIDEMIOLOGY**

Worldwide, nearly 160,000 new cases of melanoma are diagnosed every year. According to the report of the World Health Organization, nearly 57,000 deaths related to this type of cancer occur every year, with an exponential growth in melanoma cases over the past few years.

This increased incidence affects all ages and is only surpassed by liver and thyroid cancer. This elevated incidence has generated social and medical alarm, which calls for a multidisciplinary approach, essentially focused on prevention.

## **MELANOMA IN MEXICO**

Since this is a condition that manifests itself more commonly in fair-skinned individuals, in Mexico there are no accurate reports available on the disease.

The Melanoma Clinic of the National Institute of Cancer (INCAN - Instituto Nacional de Canceología) reports that the increase of this neoplasm is evident in Mexico, with an evolution of nearly 500% in the past few years. This trend is expected to continue through 2020, which will make this type of cancer increasingly common.

In our country, people with skin tumors, especially patients who suffer from melanoma, usually attend the hospital at very advanced stages, which results in a large proportion of cases not being candidates for treatment anymore owing to an important deterioration in performance status.

Melanoma is a heterogeneous oncologic entity, and it is characterized by four histopathological types: acral lentiginous, nodular, superficial spreading, and lentigo malignant melanoma. In Mexico, the most commonly occurring type is acral lentiginous melanoma, and its clinical presentation and ethnic distribution usually differentiate it from superficial spreading melanoma (the most common type of melanoma in Caucasian countries).

Acral lentiginous melanoma is the most commonly occurring melanoma in dark-skinned populations, which correspond to the III and IV skin phenotypes and which are the most prevalent phenotypes in the Mexican population.

Acral lentiginous melanoma can occur on the skin of the nail beds, palms, and soles, which are zones with little exposure to sunlight and are protected from ultraviolet (UV) radiation by a thick layer of stratum corneum. Therefore, it is highly unlikely for UV radiation to play an important role in the pathogenesis of acral lentiginous melanoma<sup>2</sup>.

# EPIDEMIOLOGICAL AND RISK FACTORS ASSOCIATED WITH MELANOMA

#### Age

Melanoma can occur at any age, although these lesions are increasingly being diagnosed in young people, with the highest frequency concentrating at middle age. Forty-one percent of melanomas are diagnosed prior to 55 years of age. After 70 years of age, the nodular and acral lentiginous types are more common (58%), whereas in younger people, superficial spreading is predominant (74%). There also seems to be a correlation between age and thickness: elderly patients have a higher Breslow index than younger ones.

#### Gender

Melanoma is slightly more common in females, where it predominates on the lower limbs and zones with higher sun exposure and, generally, the prognosis is better than in males.

#### **Racial factor**

There is a higher incidence of melanoma in blond, redhaired, and clear-eyed people. Type I and II skin.

The phototype is the skin's ability to adapt to sun exposure that each individual has since birth, i.e. the set of characteristics that determine if the skin becomes tanned or not, and how and to what extent it does.

Fitzpatrick created a six-phototype classification. Phototype I individuals have milky white skin, blue eyes, reddish hair, and freckles on the skin. Those with phototype II are individuals with white skin, blue eyes, blond hair, and freckles. Phototype III individuals belong to European Caucasian races that usually are not exposed to the sun. Those with Phototype IV have light brown skin with dark hair and eyes (Mediterranean, Mongolian and Oriental people). Phototype V individuals have brown skin (Native Americans, Hindustanis, Arabs and Hispanics). Phototype VI individuals are black-skinned persons.

Black race patients have a 10-fold lower incidence than White race individuals, and in these subjects, the most common locations are the palms, the soles, mucous membranes, and the eyes, which indicates the importance of pigmentation as a protection against melanoma.

# Presence of nevi

The existence of an elevated number of nevi is correlated with a higher probability for developing melanoma, especially if there are atypical nevi present.

Congenital giant nevi also present higher risk, especially if located on paravertebral regions. However, melanomas develop de novo in 75% of cases, with 25% developing on a preexisting nevus.

Previous existence of a melanoma increases the risk for the development of a new melanoma 70-fold. People with more than 50 common melanocytic nevi have a risk factor threefold higher than the normal population, and people with more than 100 nevi have a 7.6-fold higher risk for developing melanoma. Congenital melanocytic giant nevi have a risk for malignant transformation of 6-8%, and generally develop into melanoma before the patient is 10 years of age.

Congenital melanocytic nevi do not appear to confer an increased risk.

Atypical melanocytic nevi are a risk marker for the development of melanoma. In these cases, the risk for melanoma ranges from twofold to 28-fold, depending on the number of nevi.

# Genetic factors

When there is a family history of melanoma, there is always an up to 12-fold higher risk. Currently, two susceptibility genes for melanoma are known: the CDKN2A gene (p16), located at chromosome 9, and CDK4, located at chromosome 14. Twenty percent of the families with melanoma have mutations in CDKN2A. The development of familial melanoma associated with these mutations probably represents less than 1% of melanoma cases<sup>3</sup>.

#### Sunlight and demographic situation

There is a direct relationship between sun exposure and the incidence of melanoma and this is why it is more common in zones near the equator. However, to consider the sunlight-melanoma relationship, the patient must have experienced three or more sunburns, with blistering, before 20 years of age.

There is also no doubt that UV radiation is a risk factor for nevi and melanoma. All wavelengths involve danger, but especially those between 290-320 nm.

Indoor tanning-users receive double the irradiation than those who expose themselves to sunlight on the beach at noon and in summer. There is also higher prevalence among those people with intermittent and intense sun exposure.

#### Immunosuppression

There is higher risk for the development melanoma in patients with leukemia, lymphomas, organ transplantation, HIV infection, or any other pathological or drug-induced immunosuppression condition<sup>4</sup>.

### DIAGNOSIS

A melanoma clinical diagnosis is based on the recognition of the melanoma forms' clinical features, i.e. recognizing and identifying the transformation of a preexisting nevus by its asymmetric growth, imprecise borders, and variegated coloration with black areas and less pigmented and bluish areas representing areas of regression.

The following features are considered signs for suspicion in a pigmented lesion; (i) asymmetry; (ii) imprecise borders; (iii) changing color; (iv) diameter larger than 6 mm; (v) papular elevations on the nevus surface; (vi) family history; (vii) different thickness on different zones of the nevus; (viii) presence of hemorrhage.

When there are previously existing nevi, the detection of changes in them should also alert to the presence of melanoma. Most initial changes include the presence of coloration changes, itching, size enlargement, and satellite development. In more evolved lesions, the appearance of hemorrhage and/or ulceration can be observed<sup>5,6</sup>.

In addition to clinical examination, the performance of dermatoscopy either by means of magnifying devices or by computerized digital analysis of pigmented lesions, has increased the sensitivity in the diagnosis of melanoma-suspected lesions<sup>7,8</sup>. (Clinical Stage, Table 1)<sup>9</sup>.

# MOLECULAR FACTORS AND SERUM MARKER

Clinicopathological factors are currently the basis of clinical care. In spite of the numerous previously described factors for identification, there is still broad survival heterogeneity within clinical stages.

Several gene mutations have been associated with prognosis, including ERBB3, AKT, MITF, PTEN, BCL2, and NCOA3; however, their prognostic value has not been clarified.

Table 1         Melanoma staging system						
Clinical staging	Т	Ν	Μ			
0	Tis	N0	MO			
IA	T1a	N0	MO			
IB	T1b	N0	MO			
T2a	N0	MO				
IIA	T2b	N0	MO			
T3a	N0	MO				
IIB	T3b	N0	MO			
T4a	N0	MO				
CII	T4b	N0	MO			
III	Any T	N > N0	MO			
IV	Any T	Any N	M1			
Pathologic classifica	ation					
0	Tis	N0	MO			
IA	T1a	N0	MO			
IB	T1b	N0	MO			
T2a	N0	MO				
IIA	T2b	N0	MO			
T3a	N0	MO				
IIB	T3b	N0	MO			
T4a	N0	MO				
IIC	T4b	N0	MO			
IIIA	T1-4a	N1a	MO			
T1-4a	N2a	MO				
IIIB	T1-4b	N1a	MO			
T1-4b	N2a	MO				
T1-4a	N1b	MO				
T1-4a	N2b	MO				
T1-4a	N2c	MO				
IIIC	T1-4b	N1b	MO			
T1-4b	N2b	MO				
T1-4b	N2c	MO				
Any T	N3	MO				
IV	Any T	Any N	M1			

The serum marker that has been fully accepted owing to its prognostic value is lactate dehydrogenase (LDH). High levels of LDH have been recently associated with poor survival; in patients with advanced melanoma, it was the only tumor marker that was significantly associated with the outcome in a multivariate analysis<sup>10</sup>. This finding led to the incorporation of LDH in the staging criteria for patients with metastatic disease.

In patients with thin melanomas, the global rate of sentinel ganglion positivity is approximately 5%, which has given rise to an important debate with regard to the most adequate indications for the management of these patients<sup>11</sup>.

### CANCER AND IMMUNE RESPONSE

The humoral immune system is able to produce sufficiently diverse antibodies to recognize over 10 thousand million foreign antigens with targets as diverse as pathogenic microorganisms and tumor cells.

After binding to the antigen, the antibody effector function is mediated by the following:

- Complement fixation;
- Binding to the Fc receptor, which leads to neutrophil degranulation;
- Participation of other immune cells with cytotoxic function;
- Antibody-dependent cell-mediated cytotoxicity (ADCC) or prevention of antigens binding to adhesion or signaling molecules.

In turn, these events can promote a variety of regulating functions that modulate the immune response, including immunoglobulin-class switching, cytokine release, B-cell memory, and feedback regulation influencing on immune increase or suppression.

The adaptability and diversity of this system is closely regulated, and the B-cells that produce antibodies that bind to the antigen-free fraction are eliminated.

A T-cell effective response requires two signals: an antigen in an antigen-presenting cell binds to the T-cell receptor in a T-cell, and a molecule in the T-cell, known as CD28, interacts with another molecule in the antigen-presenting cell (APC), known as B7. This double signal helps to ensure that T-cells will attack antigens rather than healthy tissue. As a measure to protect healthy cells and minimize T-cell non-specific activation, the cytotoxic T-lymphocyte antigen 4 (CTLA-4), a molecule expressed on the surface of activated T-cells, can stop T-cell activation by forming a complex with the B7 molecule rather than with the CD28 molecule. This function, which can also inactivate T-cells, is an important barrier for antitumor immunotherapy.

In order for the immune system to be able to assemble an efficacious response against cancer, a series of systematized events has to occur. The basis of this immune response has been elegantly described by Chen and Mellman as a "cancer-immunity cycle".

The discovery of CTLA-4 and its crucial function on T-cells effector function inhibition provided the first indication that negative signals might regulate T-cell tolerance. The value of this approach has been translated in numerous occasions into clinical medicine to produce agents that interact with the immune system.

#### THE IMMUNE SYSTEM IN MELANOMA

Therapeutic antibodies have been used in medical care and research for decades, but over the last 15 years they have become commonly used in cancer management. Most of these monoclonal antibodies are antagonistic, and were designed to block an antigen of the targeted protein or to induce ADCC.

The knowledge of T-cell receptors and regulating pathways rapid expansion, natural-killer (NK) cells and APC, has identified the targets the current generation of therapeutic antibodies against melanoma is directed to.

The T-cell pathways that have been more widely studied for the development of therapeutic antibodies in cancer are the T-cell checkpoints known as CTLA-4 (designated CD152) and programmed cell death protein-1 (PD1, designated CD279).

A pivotal trial of ipilimumab, a human monoclonal antibody against CTLA-4, in patients with metastatic melanoma showed a significant improvement in median overall survival of 10 months, in comparison with 6.4 months in control patients (hazard ratio [HR] for death: 0.68; p < 0.001) and led to this agent's first approval in the USA in 2011.

The analysis of long-term survival results has been promising. Data obtained from 4,846 patients who received ipilimumab in 12 trials (as part of a clinical trial or an expanded access program) showed a survival plateau after approximately three years of treatment for 21% of patients, which continued for up to 10 years in some patients<sup>13</sup>.

# TREATMENT OF MELANOMA

Early diagnosis is essential for the cure of melanoma. With regard to its treatment, there are basically three options: surgery, adjuvant treatment, and metastatic melanoma treatment.

#### Surgical treatment

Removal of the melanoma when it is confined to the epidermis and does not surpass the basement membrane brings 100% survival. When the melanoma ruptures the basement membrane and initiates its vertical growth phase, the prognosis worsens and treatment of the primary tumor, lymph node involvement and metastasis, if present, should be implemented.

Initial surgical treatment involves broad resection down to the muscle fascia, with a 1-3 mm normal skin margin. After initial biopsy-resection, and once basic data such as Breslow thickness are known, a 1-2 cm broadening of the resection margins is then performed. The purpose of this broadening is to reduce the possibility of tumor relapse and residual disease.

With regard to lymph node involvement, the presence or not of regional lymph node metastasis in patients with melanoma has a prognostic value, and the risk for the development of lymph node metastasis is related to the thickness of the primary tumor, as previously described.

In situ tumors do not entail risk, thin tumors ( $\leq$  1 mm) have low risk (< 5%), and medium thickness tumors (1-4 mm)

have a 20-25% risk for lymph node metastases. In patients in whom the presence of lymph node involvement is clinically detected by palpation, extirpation has to be carried out by therapeutic lymph node resection.

In patients at risk for the development of lymph node metastases but without clinical evidence of such an involvement, resection of the regional lymph node chain can be carried out with the purpose to remove existing but clinically occult lymph node metastases, which is known as elective lymph node resection. However, elective lymphadenectomy has been practically left behind in favor of sentinel lymph node resection. Lymphadenectomy is only completed if the sentinel lymph node is affected.

In order to be able to differentiate between patients with clinically occult lymph node involvement and patients without lymph node metastasis, the sentinel lymph node biopsy has been developed, since this is the most sensitive and specific technique for lymph node staging and constitutes the most important predictor of survival, and it is of great value for therapeutic decision making.

This technique is indicated for melanomas larger than 1 mm, or for those that, being smaller than 1 mm, meet any of the following criteria: Clark level higher than III-V, presence of mitosis, vascular invasion, microsatellitosis, ulceration or histological signs of regression.

More than half the patients with tumors larger than 4 mm have lymph-node involvement<sup>11</sup>.

#### Adjuvant treatment

The rationale for adjuvant treatment after surgery is based on the poor prognosis of high-risk patients, with relapse rates ranging from 50 to 80%. Many types of treatment have been used: chemotherapy, unspecific immune therapy (treatment with Calmette-Guerin bacillus), active specific immune therapy, immunochemotherapy, isolated chemotherapy perfusion on a limb for melanomas of extremities, and radiotherapy. However, none of these treatment modalities has improved patient survival.

High-risk patients (stages IIB, IIC and III) should be assessed for adjuvant therapy with high-dose interferon- $\alpha$ 2b, since this is the only agent that currently has shown an improvement in disease-free survival and overall survival.

The most widely used scheme in our setting is highdose administration, which involves an induction with intravenous interferon- $\alpha$ 2b at a 20 MU/m<sup>2</sup> dose five days a week for four weeks, followed by maintenance treatment with subcutaneous interferon- $\alpha$ 2b at a dose of 10 MU/m<sup>2</sup> three days a week for 48 weeks. The side effects of this treatment are not innocuous (only 60% of patients complete the treatment in the best series); asthenia, flu-like syndrome, liver enzyme abnormalities, depression, myelosuppression, and vitiligo, etc. are reported as important toxicities. The indication is recommended for patients with good general status and absence of significant comorbidity.

Radiotherapy may contribute to reduce the number of local relapses. It is indicated in cases of affected margins, lymph nodes with extra-nodal invasion, more than four involved lymph nodes, size of affected lymph node larger than 3 cm, or satellitosis.

# TREATMENT OF RECURRENT OR METASTATIC MELANOMA

### Chemotherapy

Dacarbazine was approved in 1970 based on overall response rates. In phase III trials, an overall response rate of 10-20% is reported, with complete responses being observed on few occasions. The effect on overall survival has not been demonstrated in randomized trials<sup>14</sup>.

Temozolomide is an oral alkylating agent that appeared to have similar effects to intravenous dacarbazine in a randomized phase III trial where the primary endpoint was overall survival; however, since the trial was designed to demonstrate temozolomide superiority, which was not accomplished, the sample size was not sufficient to prove statistical non-inferiority.

#### Local palliative therapy

Melanomas that metastasize to distant sites with lymph nodes present can be palliated with regional lymphadenectomy. Isolated metastases to the lung, gastrointestinal (GI) tract, bone, or sometimes to the brain can be palliated by means of resection, with occasional long-term survival<sup>15</sup>.

## SIGNAL TRANSDUCTION INHIBITORS

In studies conducted to date, both BRAF and MEK inhibitors have been shown to have considerable effect on the natural evolution of melanoma, although they do not appear to be curative as single drugs.

#### **BRAF** inhibitors

Currently, the treatment of disseminated disease must be preceded by the determination of BRAF V600E mutation in tumor tissue.

Approximately 50% of skin melanomas show activation of mutations in BRAF. This enables the treatment with tyrosine kinase-specific inhibitors such as vemurafenib or dabrafenib. Both drugs are superior to standard chemotherapy in response rates, time to progression, and overall survival. They are orally administered every day: vemurafenib at 960 mg every 12 hours and dabrafenib at 150 mg every 12 hours.

The MEK inhibitors, such as trametinib and cobimetinib, are also useful to treat melanomas harboring mutations in BRAF. Recently, the combination of one BRAF and one MEK inhibitor has been shown to be superior to either of them separately, with survival being improved, which has led to the combination becoming the usual treatment of BRAF-mutated melanoma.

#### Vemurafenib

Approved by the US Food and Drug Administration (FDA) in 2011, it demonstrated an improvement of PFS and OS in patients with unresectable or advanced disease. Vemurafenib is a classic drug, a selective inhibitor of BRAF V600E kinase. It is formulated for oral administration, and its indication is limited to patients with mutation identified by means of an FDA-approved test.

## Dabrafenib

A classic drug, BRAF selective inhibitor, formulated for oral administration, dabrafenib was approved by the FDA in 2013. It demonstrated an increase in progression-free survival when compared with dacarbazine in the international, multi-center BREAK-3 trial.

# **MEK** inhibitors

# Trametinib

Trametinib, a classic drug and MEK1 and MEK2 selective inhibitor, formulated for oral administration, was approved by the FDA in 2013 for patients with unresectable or metastatic melanoma with V600E or K mutations in BRAF.

# COMBINED SIGNAL TRANSDUCTION THERAPY

In 2014, the FDA fast track approved the dabrafenib plus trametinib combination for patients with unresectable or metastatic melanomas, carriers of the V600E or V600K mutation in BRAF. The combination demonstrated better rates of durable response in comparison with dabrafenib monotherapy. Full approval is pending on the results of ongoing clinical trials demonstrating clinical benefit on overall survival<sup>16</sup>.

# **C-KIT INHIBITORS**

Preliminary data suggest that mucosal or acral melanomas with c-KIT-activating mutations or amplification may be sensitive to a variety of c-KIT inhibitors. There are phase II and III trials available in patients with stage III or IV unresectable melanoma harboring a mutation in c-KIT<sup>17</sup>.

# IMMUNOTHERAPY

Different immunotherapy strategies have been described, including:

- Non-personalized immunotherapy, e.g. monoclonal antibodies against tumor antigens (anti-CD19, CD20);
- Antitumor response-potentiating cytokines (IL-2, IFN-α);
- Inhibitory receptor-blocking antibodies (PD-1, CTLA-4).

# Anti-CTLA-4 clinical results

# Ipilimumab

Ipilimumab is a fully human IgG1 monoclonal antibody that binds to the CTLA-4 receptor expressed in activated T-cells. Biologically active and tolerable doses were established for ipilimumab in phase I and II studies. These early studies also established that patients with advanced melanoma had objective tumor regressions.

Two randomized phase III trials with ipilimumab were carried out in patients with advanced melanoma. The first trial was conducted in patients with metastatic melanoma; the eligibility criterion of HLA-A\*0201 expression was to enable the comparison of ipilimumab with a gp100 peptide vaccine in the control group. The gp100-specific peptides contained in the vaccine are only recognized in the HLA-A\*0201 context. The patients were randomized to treatment groups at a 3:1:1 ratio to ipilimumab (3 mg/kg IV every three weeks for four doses) and the gp100 vaccine, ipilimumab monotherapy plus placebo, or gp100 monotherapy plus placebo, respectively. Objective response rates were low, but there was no statistically significant survival improvement in ipilimumab-treated patients<sup>18</sup>.

Unlike chemotherapy where tumor regression is usually evident in a few weeks, melanoma regression after treatment with ipilimumab usually takes many weeks, and sometimes months, after the completion of therapy. Late responses to ipilimumab or rapid progression followed by marked regression (pseudo-progression) have also been reported.

The recognition of marked differences in tumor response kinetics after anti-CTLA-4 in comparison with chemotherapy and other immunotherapies has modified clinical practice.

These observations have led to alternate measurement rules to assess clinical response, known as "immune response-related criteria", although currently there is no validated criterion<sup>19</sup>.

The FDA approved ipilimumab in March 2011 for patients with metastatic melanoma or unresectable disease. This was the first approval of a drug that has demonstrated a survival benefit in a randomized phase III trial for patients with unresectable or metastatic advanced melanoma.

Ongoing phase III studies are also investigating ipilimumab in other malignancies such as metastatic prostate cancer by including antibodies in immune checkpoints (Table 2)<sup>20</sup>.

## Tremelimumab

Tremelimumab is a fully human IgG2 monoclonal antibody that has also been tested in patients with melanoma, but it

Table 2. Summary of long-term results for ipilimumab in metastatic melanoma

	Schadendorf, et al.	Ascierto, et al.
Treated patients	1,861	833
Median survival (months)	11.4	7.2
1-year survival (%)	44	35
2-year survival (%)	28	20
Immunity-related toxicity (%)	14	33

'	1			
Nivolumab + ipilimumab <b>regimen (mg/kg)</b>	1-year overall survival (%)	2-year overall survival (%)	Mean overall survival (months)	Median progression-free survival (weeks)
All concurrent (n = 53)	85	79	40	27
0.3 + 3 (14)	57	50	27	13
1 + 3 (17)	94	-	NR	58
3 + 1 (16)	94	-	NR	34
3 + 3 (6)	100	_	NR	34

Table 3. Response duration in patients who received concurrent ipilimumab plus nivolumab

NR: not reached; -: no reported data.

has not yet been approved by the FDA and other regulatory agencies for cancer therapy.

Tremelimumab has a longer plasma half-life than ipilimumab (22 vs. 15.4 days) and the IgG2 subtype has less binding affinity to the Fc gamma receptor (Fc $\gamma$ R) in macrophages.

The results of a comparison in a phase III trial of tremelimumab (15 mg/kg IV every 90 days) vs. dacarbazine or temozolomide in patients with metastatic melanoma have been reported, with no differences between tremelimumab and chemotherapy in the objective response (10.7 vs. 9.8%) or overall survival (12.4 vs. 10.7 months). However, the response duration was significantly longer with tremelimumab (35.8 vs. 13.7 months)<sup>19,20</sup>.

# Anti-PD-1 clinical results

The first anti-PD-1 antibody tested in patients with melanoma was MDX-1106, a fully human IgG4, currently known as nivolumab. This antibody blocks PD-L1 and PD-1 interaction, as well as the interaction between PD-1 and CD80 found in B-cells and macrophages, the normal function of which is to provide a co-stimulating signal when CD28 is involved in activated T-cells<sup>21</sup>.

Nivolumab was compared with dacarbazine in a randomized trial in 418 patients with non-BRAF-mutated melanoma without previous systemic treatment. The group that received nivolumab (n = 210) had significantly better objective response (40 vs. 13.9%), one-year survival (72.9 vs. 42.1%) and progression-free survival (5.1 vs. 2.2 months) in comparison with patients receiving dacarbazine<sup>22</sup>.

Another antagonist antibody to specifically compete with the interaction between PD-1 and PD-L1 and PD-L2, known as pembrolizumab, has been studied in melanoma. This antibody, also a fully human IgG4, was tested in 173 patients with unresectable or metastatic melanoma who had disease progression after having received at least two ipilimumab doses and were treated with pembrolizumab at 2 mg/kg (n = 89) or 10 mg/kg (n = 84).

Objective response was 26% for both dose levels, with a mean time to response of 12 weeks. Median response duration has not been reached at the time of publication. Immune-mediated toxicities were also observed, but with less severity and incidence in comparison with anti-CTLA-4. Fatigue (33%), itching and rash were the most common toxici-

ties and did not differ when the 2 and 10 mg/kg dose levels were compared.

Pembrolizumab was approved by the FDA in September 2014 for the treatment of patients with advanced melanoma progressing after ipilimumab or BRAF-targeted therapy in patients whose melanomas express a BRAF mutation. Currently, there are more than 85 clinical trials investigating anti-PD-1 or anti-PD-L1 monotherapy or combinations in patients with metastatic melanoma, bladder cancer, nonsmall cell lung cancer, and renal cancer, which may result in additional indications for this immunotherapy<sup>23</sup>.

# COMBINATION THERAPY WITH ANTIBODIES

As previously detailed, monotherapy using CTLA-4, PD-1 or PD-L1 antagonistic antibodies can induce significant tumor regression and improve survival in patients with melanoma as well as with other malignancies.

In a phase I study, which investigated ipilimumab and nivolumab sequential and concurrent administration, 17 out of 53 patients received concurrent therapy at ipilimumab and nivolumab maximum tolerated doses (3 and 1 mg/kg, respectively). Objective response in this group was 53%. Tumor regression occurred within the first 12 weeks in the majority of responders (Table 3)<sup>24</sup>.

# PROBLEM STATEMENT

What are the clinical results of the use of ipilimumab in patients diagnosed with recurrent or metastatic melanoma treated at the ABC Medical Center?

#### HYPOTHESIS

Are there any factors to identify overall survival and progression-free survival in ipilimumab-treated patients?

#### **GENERAL OBJECTIVE**

To describe the clinical course of patients treated with ipilimumab at the ABC Medical Center.

# SPECIFIC OBJECTIVE

To describe overall survival of patients diagnosed with metastatic or recurrent melanoma treated with ipilimumab at the ABC Medical Center.

# **STUDY DESIGN**

- Available population;
- Selection criteria;
- Variables.

# MATERIAL AND METHODS

#### Sample size

Patients were selected from the period between 2012 and 2015 at the ABC Medical Center by reviewing medical records.

# Inclusion and exclusion criteria

# Inclusion criteria:

- Females and males;
- Older than 18 years of age;
- Metastatic or recurrent melanoma diagnosis;
- ABC Medical Center patients diagnosed with metastatic or recurrent melanoma treated with ipilimumab at 3 mg/kg every three weeks for four sessions;
- Patients with ABC Medical Center cancer center medical records available;
- Patients who have completed four cycles of ipilimumab every three weeks at 3 mg/kg;
- Laboratory tests one week prior to ipilimumab initiation and one week after completing the fourth ipilimumab administration;
- Patients with imaging studies available to classify treatment response assessment.

# Exclusion criteria:

- Patients with incomplete data;
- Pediatric populations;
- Patients without histopathological report and/or laboratory tests;
- Patients without imaging studies for response assessment.

# Definition of variables

#### Baseline variables

- Conceptual;
- Operative;
- Type of variable: continuous quantitative;
- Measurement.

# Study variables

- Age;
- Gender;
- Histological variety;
- Primary site;
- Previous treatment;
- Previous chemotherapy;
- Immunotherapy;
- Treatment with ipilimumab;
- Toxicity to ipilimumab;
- Progression-free interval;
- Overall survival;

# Methodology

## Sample size calculation

Non-random, convenience sampling of consecutive cases meeting the inclusion criteria.

# Statistical analysis

Descriptive statistics with central tendency and dispersion measures were used. Categorical variables were expressed with absolute and relative frequency measures, whereas linear variables were presented as means and standard deviations or medians with interquartile ranges, according to frequency distribution behavior.

Hypothesis testing for linear variables assessment was carried out using Student's t-test or Mann Whitney's U-test for independent samples, or univariate ANOVA or Kruskal-Wallis test. Categorical variables were analyzed with the chi-square test or Fisher's exact test.

The survival analysis was made with Cox regression models and was represented using Kaplan-Meier estimates for overall survival and progression-free survival. Strength of association measurements were expressed as odds ratios (OR) and 95% confidence intervals (CI).

Statistical significance was considered at a two-tailed adjusted alpha error lower than 5%. The software pack used was STATA Special Edition V 11.1.

# RESULTS

## Socio-demographic characteristics

Thirteen patients were included, out of which 53% (7/13) were females and 46% (6/13) males, with median age at diagnosis of 54 years (interquartile range [IQR] of 47-73). Demographic characteristics included 53.8% (7/13) Caucasian and 46.2% (6/13) Hispanic ethnicity (Table 4).

# Baseline disease characteristics, diagnostic approach and clinical presentation

Clinical status (CS) I, three patients (23.1%); CSII, three (23.1%); CSIII, four (30.8%); CSIV, three (23.1%); the detailed clinical status is shown in table 4. Histological lineages, in

order of frequency, were: nodular in 69.2% (9/13), superficial spreading in 15.4% (2/13), mucosal in 7.7% (1/13), and unidentified in 7.7% (1/13) of patients. Primary site was the limbs in seven (53.8%), trunk or back in four (30.8%) and nasal mucosa in one (7.7%).

Breslow and Clark values had a median of 3.5 mm (0.8-4.5) and grade 4 (IQR: 2-4), respectively. Lesion ulceration and lymphovascular invasion was found in 38.5 and 30.8%, respectively. The BRAF V600 mutation was present in 30.8% (4/13) of patients.

Metastatic disease was recorded in 15.4% (2/13) of patients at diagnosis, with the site of metastasis being the central nervous system (CNS) in both observed cases (Table 4).

# Clinical evolution and treatment

Total median follow-up time of the population was 18 months (IQR: 8-24), with CNS involvement being found in six patients (46.2%), locoregional recurrence in 61.5% (8/13), and distant recurrence in 15.4% (2/13). Visceral metastatic activity was found in 46% of cases, with the most common sites being the lung in 38% (5/13) and the liver in 23% (3/13) of patients. Median time to recurrence was 18 months (IQR: 11-78).

All patients were treated with ipilimumab at 3 mg/kg every three weeks for four sessions. Fifty-three percent of patients had received some treatment prior to ipilimumab initiation: interferon was received by 37.5% (3/8), vemurafenib by 25% (2/8), adjuvant radiotherapy by 25% (2/8), and unknown by 12% (1/8). Median time interval between initial-stage diagnosis and ipilimumab initiation was 29 months (IQR: 10-48).

Overall survival and progression-free survival had a median of 18 (IQR: 8-24) and five months (IQR: 4-24), respectively. The interval between diagnosis and reassessment by PET had a median of 28 months (IQR: 8-72), and 61.5% (8/13) of patients died during the follow-up period (Fig. 1).

Table 4.	Baseline	general	and	demographic
character	istics (n =	= 13)		

Characteristic	n (%)
Female gender	7 (53)
Age, median (IQR), years	54 (47-73)
ECOG 0-1	13 (100)
Caucasians	7/13 (53.8)
Hispanics	6/13 (46.2)
BRAF V600 mutation	4 (30.8)
M1c	1 (10)
CNS metastasis, during follow-up	6 (60)
Stage I	3 (23.1)
Stage II	2 (15.4)
Stage IIC	1 (7.7)
Stage III	2 (15.4)
Stage IIIA	1 (7.7)
Stage IIIB	1 (7.7)
Stage IV	3 (23.1)

C.P. Camacho-Limas, et al.

Table 5. General laboratory tests (n = 13)\*

Hemoglobin, g/dl	14.4 (15.5-13.8)
Platelet, number/cm <sup>3</sup>	278 (294-224)
Absolute neutrophils, cells/cm <sup>3</sup>	5.3 (5.9-4.6)
Total lymphocytes, cells/cm <sup>3</sup>	1.20 (1.5-1.04)
LDH, IU/dl (at enrollment)	391.5 (594.5-291.5)
LDH, IU/dL (final)	370 (856-273)
Glucose, mg/dl	85 (99-75)
Creatinine, mg/dl	0.8 (0.9-0.7)
BUN, mg/dl	15 (16- 12)
Albumin, g/dl	4.1 (4.4-3.9)
Globulin, mg/dl	2.6 (3.0-2.4)
Albumin/globulin ratio	1.4 (1.6-1.2)
Total cholesterol, mg/dl	150 (176-142)
Triglycerides, mg/dl	127 (177-91.0)
AST, IU/dl	24 (25-18)
ALT, IU/dl	21 (36-17)
GGT, IU/dl	108.5 (201-16)
Alkaline phosphatase, IU/dl	79 (98-66)
Total bilirubin, mg/dl	0.9 (1.0-0.7)
Direct bilirubin, mg/dl	0.45 (0.6-0.20)
Indirect bilirubin, mg/dl	0.40 (0.70-0.20)
Total protein, mg/dl	7.0 (7.5 6.8)

\*Values expressed as the median and interquartile range (IQR). ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; GGT: gamma-glutamyl transferase; LDH: lactate dehydrogenase.

No statistically significant differences were found between the remaining clinical or demographic variables, clinical presentation, or laboratory tests and overall mortality during the follow-up period. Laboratory tests, therapeutic response characteristics, and histological patterns according to patient group are described in tables 5, 6 and 7.

During treatment, data consistent with pseudo-progression were found in 50% (6/12) of patients and progressive disease in 50%, whereas in week 12 reassessment, complete response was observed in 7.7% (1/13), partial response in 15.4% (2/13), stable disease in 7.7% (1/13), and progressive disease in 61.5% (8/13) (Table 3).

# Factors associated with patient response to the treatment with ipilimumab

Hispanic ethnicity was identified as a protecting factor against progression in ipilimumab-treated patients (OR: 0.14; 95% CI: 0.23-0.87; p = 0.015) (Fig. 1).

Median progression-free interval in responders vs. non-responders was 30 (IQR: 14.5-48) vs. 4 weeks (IQR: 3-5); p = 0.37 (Fig. 2).

#### DISCUSSION

From November 2014 onwards, there were 830 clinical trials appearing at the National Institute of Cancer website un-

Table 6.	Therapeutic	response	characteristics	(n =	13)
----------	-------------	----------	-----------------	------	-----

Response characteristics*	n (%)
Overall survival	18 (8-24)
Progression-free survival	5 (4-24)
Complete response	1 (7.7)
Partial response	2 (15.4)
Stable disease	1 (7.7)
Progressive disease	8 (61.5)
*Months, median (IQR).	

der the search term "immunotherapy" and 55 of these trials were in patients with melanoma.

The courage of many of these melanoma patients who voluntarily offered to participate in clinical trials has been highly valuable for the development of T-cell antibody therapy, but most of these patients do not get cured and sequentially participate in clinical trials when the melanoma progresses.

However, melanoma progression remains the most common clinical scenario. Having robust predictive markers to better determine the clinical approach would be ideal, but, currently, careful evaluation of the patient performance status, an open discussion on goals and options, and a doctor experienced in response to immunotherapy are the best approach to navigate these complex clinical scenarios.

In this retrospective review of 13 ipilimumab-treated patients, we observed that 23% (3) of patients showed an objective response with ipilimumab-based treatment: one patient with complete response and two patients with partial response, in addition to one patient with stable disease and eight patients (corresponding to 61.5%) with progressive disease after four cycles and clinical and imaging assessment after 12 weeks, with responders acquiring an overwhelming importance with an overall survival of more than 18 months (Fig. 3 and 4).

On the other hand, as previously mentioned, nodular melanoma is the second form of melanoma in terms of frequency and accounts for 10-15% of melanoma cases overall, and in this analysis, 80% of responders were observed to have this histological variety.

It should be noted that ethnic distribution according to the medical records review was skin phototype I and II, and responders had skin type III and IV, although no biochemical associations were found in that regard.

In relation to toxicity with ipilimumab, a review of the medical records revealed an adequate tolerance to immunotherapy, with fatigue being the most common side effect



Figure 1. Kaplan-Meier estimator for overall survival in patients with metastatic melanoma treated with ipilimumab (n = 13).



Figure 2. Kaplan-Meier estimator for progression-free survival in patients with metastatic melanoma treated with ipilimumab (n = 13).

(26%), followed by rash (8%), which is consistent with findings reported in the literature (fatigue in 36.1% and rash in 17.6%).

There are many unanswered questions about the future of antibody therapy for its use in melanoma, and considering that there are favorable results in different studies with the anti-CTLA-4 and anti-PDL1 combination, the use of

Table 7. Histological type comparison and type of response to ipilimumab							
Histological type	Non-responders $(n = 7)$		Responders $(n = 5)$		Р		
Histological type	n	%	n	%	NS		
Nodular (n = 8)	4	57.1	4	80.0	NS		
Superficial spreading $(n = 2)$	2	28.6	0	0.0	NS		
Mucosal (n = 1)	0	0.0	1	20.0	NS		
Unidentified $(n = 1)$	1	14.3	0	0.0	NS		

60-50-30-20-10-0-Non-responders Type of response

Figure 3. Type of response and overall survival.



Figure 4. Type of response and progression-free interval.

ipilimumab as monotherapy is likely to become a secondary option.

The approach of antibodies targeting T-cell regulation pathways has been clearly shown to amplify antitumor activity, and this has revolutionized the treatment of melanoma, thus leaving a future window of opportunity for our patients with this condition.

The mechanisms for prolonged stability or delayed regression in some patients are not known, but they may be related to T-cell tumor infiltration after anti-CTLA-4.

# CONCLUSIONS

In this cross-sectional analysis, findings published so far on ipilimumab treatment for metastatic or recurrent melanoma were corroborated, with a response rate of 23%, fundamentally characterized by a response duration of more than 28 months until current follow-up in patients who showed an objective response with the use of ipilimumab.

# DECLARATION OF INTEREST

The present publication does not confer any type of conflict of interests.

# REFERENCES

- Secretaría de Salud. Dirección General de Epidemiología. Registro Histopatológico de Neoplasias Malignas, 2001. http://sinais.salud.gob.mx/.
- Martínez-Saíd H, Cuéllar-Hubbe M, Barrón-Velásquez E, Padilla RA, Herrera-Gómez A, López-Graniel CM. Epidemiology of cutaneos melanoma in México (1982-2002). Eur J Surg Oncol. 2004;30:163.
- Curin AJ, Fridlyand J, Kageshita T, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med. 2005;353:2135-47.
- Rosas SH, Baca T, Muñoz D, Muñoz F, Muñoz G. Estudio clínico, epidemiológico e histopatológico de melanoma maligno. Serie de 31 Casos. CIMEL. 2003;8:23-7.
- Martínez SH. El primer Consenso Nacional de Expertos en Melanoma. Gac Mex Oncol. 2005;4:11-13.
- Dennis LK. Analysis of the melanoma epidemic, both apparent and real. Arch Dermatol. 1999;135:275-80.
- Wong JH, Wanek L, Chang LJ, Goradia T, Morton D. The importance of anatomic site in prognosis in patients with cutaneous melanomas. Arch Surg. 1991;126:486-9.
- Martínez-Said H, Gutiérrez-Vidrio RM, Orozco Topete RL, et al. Manejo de la lesión primaria por melanoma cutáneo. Gac Mex Oncol. 2005;4(Supl 2):18-19.
- 9. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification J Clin Oncol. 2009;27: 6199-206.
- Bartlett EK, Karakousis GC. Current staging and prognostic factors in melanoma. Surg Oncol Clin N Am. 2015;24:215-27.
- Bartlett EK1, Gimotty PA, Sinnamon AJ, et al. Clark level risk stratifies patients with mitogenic thin melanomas for sentinel lymph node biopsy Ann Surg Oncol. 2014;21:643-9.
- Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013;39:1-10.
- The Role of Anti-PD-1/PD-L1 Agents in Melanoma: Progress to Date, University of California San Francisco (UCSF), San Francisco, USA 2015.
- Chapman PB, Einhorn LH, Meyers ML, et al. Phase III multicenter randomized trial of the Dartmouth regimen versus dacarbazine in patients with metastatic melanoma. J Clin Oncol. 1999;17:2745-51.
- Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol. 2000:18: 158-66.
- A Study Comparing GSK2118436 to Dacarbazine (DTIC) in Previously Untreated Subjects With BRAF Mutation Positive Advanced (Stage III) or Metastatic (Stage IV) Melanoma NCT01227889. Available at: https:// clinicaltrials.gov/ct2/show/NCT01227889.
- Hodi FS, Friedlander P, Corless CL, et al. Major response to imatinib mesylate in KIT-mutated melanoma. J Clin Oncol. 2008;26:2046-51.
- Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011;364:2517-26.
- Curran MA, Montalvo W, Yagita H, et al. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci USA. 2010;107:4275-80.
- Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366:2455-65.
- Ribas A, Kefford R, Marshall MA, et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. J Clin Oncol. 2013;31:616-22.
- Taube JM, Klein A, Brahmer JR, et al. Association of PD-1 PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy Clin Cancer Res. 2014;20:5064-74.
- Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013;369:122-33
- Curti BD, Urba WJ. Clinical deployment of antibodies for treatment of melanoma. Mol Immunol. 2015;67:18-27.



SOCIEDAD MEXICANA DE ONCOLOGÍA, A.C. GACETA MEXICANA DE ONCOLOGÍA WWW.gamo-smeo.com



# Latissimus Dorsi Myocutaneous Extended Flap in the Reconstruction of Large Chest Wall Defects after Extensive Resections in Breast Pathology

Francisco Miguel Said-Lemus<sup>1,\*</sup>, Guillermo G. Peralta-Castillo<sup>2</sup>, Jorge A. Salazar-Andrade<sup>2</sup>, Antonio Maffuz-Aziz<sup>2</sup>, Santiago Sherwell-Cabello<sup>2</sup> and Santiago Rodríguez-Cuevas<sup>2</sup>

<sup>1</sup>Department of Plastic and Reconstructive Surgery and <sup>2</sup>Department of Breast Surgery; Instituto de Enfermedades de la Mama FUCAM, FUCAM, Mexico City, Mexico

Received for publication: 13 February 2017; accepted for publication: 25 February 2017 Available online: 10 July 2017

## **KEYWORDS**

Breast; Skin coverage; Breast reconstruction; Myocutaneous flap; Latissimus dorsi Abstract Locally advanced breast cancer remains a major problem in developing countries and it is a common presentation of this condition worldwide. In Mexico, 45% of breast cancer cases are diagnosed at locally advanced stages. Cutaneous coverage of the chest wall after extensive resection in breast cancer patients has always been a challenge for the surgical team, and latissimus dorsi flap is therefore widely used for chest wall reconstruction. With the classic technique, the size of the skin flap is usually not larger than 10 cm. For this reason, the use of latissimus dorsi extended flap has been implemented in our institution with the purpose to cover large defects of up to 40 cm. A retrospective study was carried out of all latissimus dorsi extended flap cases over a five-year period. A total of 30 patients have undergone reconstruction with a *latissimus dorsi* flap, out of which 15 were treated with the extended technique, with tumor resections of up to 30 cm being achieved. Mean age was 42.6 years. Recorded tumor dimensions were as large as 30 cm. There was a low rate of complications requiring surgical re-intervention (6.6%) throughout an average 15.8-month follow-up. This technique is reproducible and is carried out in a single surgical procedure, and can be considered for partial or total reconstruction of large esthetical defects for purely palliative or curative purposes. The success of this technique depends on adequate patient selection and multidisciplinary treatment coordinated between breast and plastic surgeons. (creativecommons.org/licenses/ by-nc-nd/4.0/).

PERMANYER

\*E-mail for correspondence: fmsaid@hotmail.com (F.M. Said-Lemus)

http://dx.doi.org/10.24875/j.gamo.17000003

1665-9201 / © 2017 Sociedad Mexicana de Oncología. Publicado por Permanyer México. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

# INTRODUCTION

Breast cancer has a great impact on women's health. It is the most common type of cancer worldwide, with more than one million new cases every year. In spite of an increased incidence, mortality related to this condition has decreased in developed countries<sup>1,2</sup>. The probability for developing invasive cancer in women is 12.03% during their lifetime (one in every eight women)<sup>3</sup>. Annually, approximately 178,480 women are diagnosed with invasive breast cancer in the USA, which represents approximately 32% of all cases of cancer in women<sup>4,5</sup>. In Mexico, this condition occupies the first place as malignancy-related cause of death since 2006, ousting cervical cancer from this position<sup>6</sup>.

The American Joint Commission on Cancer (AJCC) published the latest revision of its staging system in 20167, which is based on three parameters: tumor size (T), lymph node status (N), and presence of metastasis (M). In this system, patients are clinically (c) or pathologically (p) assigned to a tumor, node and metastasis stage. In general terms, the higher the grade is, the worse the prognosis will be<sup>8</sup>. Unfortunately, the most advanced stages remain a common presentation form in developing countries, and less so in developed countries<sup>9</sup>. In the USA, it accounts for 5-10% of newly diagnosed carcinomas, whereas in our country, according to data of the Institute of Breast Diseases, it accounts for 45% of cases at diagnosis<sup>10,11</sup>. This includes patients with large tumors with fixation to the chest wall or skin ulceration. It is important to consider that a percentage of these patients are young women (younger than 40 years) who are carriers of voluminous, ulcerated tumors, or with fixation to the chest wall<sup>12-14</sup>.

In many locally advanced breast cancer cases, initial radical surgery may be indicated since skin and/or chest wall involvement can be extensive, have ulceration and bleeding, or progress on neoadjuvant treatment. It is for this reason that in some cases, extensive resections and reconstructive surgery procedures are required in order to cover vital structures and to ensure adequate wound healing. Some indications include: radionecrosis, tumors affecting the fascia, muscle and occasionally the ribs, and tumors with important bleeding<sup>15,16</sup>. Resection and skin coverage can also improve the quality of life of patients with advanced breast cancer since it provides a palliative effect in tumors with extensive necrosis<sup>17</sup>.

Chest wall reconstruction after extensive resection has always been a challenge for the surgical team. There are different techniques described for this purpose, each one indicated according to the requirements of the defect to be corrected. The selection of this technique mainly depends on the size of the wound and type of tissue. In addition, patient prognosis should always be considered in decision making. The main objective is to reestablish coverage and protection of intrathoracic structures, sometimes with an acceptable esthetical result<sup>18</sup>.

The *latissimus dorsi* flap has been widely used for chest wall reconstruction since 1897, and was initially described by the Italian surgeon Tasini. One of the first fasciocutaneous flaps of the thoracoabdominal ipsilateral area was described by Tai, et al. in 1974, and it was irrigated by the superior epigastric artery<sup>19</sup>. Subsequently, and after better understanding of the anterior and lateral abdominal wall

vascular anatomy, flaps with subcostal, intercostal, or lumbar irrigation were described, and by the mid 80's, muscle and skin-muscle flaps became the gold standard for chest wall reconstruction<sup>20,21</sup>.

Latissimus dorsi flap is widely used in chest wall reconstruction, mainly in breast cancer patients<sup>22</sup>. The thoracodorsal vessels normally provide the blood supply of the pedicle for the *latissimus dorsi* flap, usually allowing for a large muscle portion to be mobilized. However, the size of the skin portion is often not too large, and the skills to close the donor site dictates the size of the flap; therefore, the usual size of the skin is generally not larger than 10 cm in the described classic techniques<sup>17,23,24</sup>. For this reason, the classic technique has been modified at the FUCAM Institute of Breast Diseases in order to obtain larger skin flaps that allow for large chest wall defects to be reconstructed after breast cancer-related resections.

# MATERIAL AND METHODS

A retrospective study was carried out using the prospective database of the FUCAM Institute of Breast Diseases of all identified cases of reconstruction with *latissimus dorsi* extended flap from January 2011 through June 2016. Assessments on patient demographics, tumor size, and diagnosis as well as the rate and type of complications are presented. In addition, the employed surgical technique is described and analyzed.

#### Preoperative planning

The *latissimus dorsi* extended flap is intended to provide skin coverage with or without breast reconstruction criteria, without the need to demarcate a skin bridge between the dorsal region and the chest anterior wall.

The first step is the marking of the patient by the surgeon who will perform the resection together with the surgeon in charge of the reconstruction in order to identify the limits of the resection zone, which will depend on the extension of the pathology to be treated (Fig. 1 A). This marking is made using the same criteria as for conventional *latissimus dorsi* flap, with the anatomic variation that the lower lateral border of the defect will become the flap distant portion, since blood supply is determined by perforating arteries, the perforator vessels of which project to the anterior portion, which results in extended skin islands of up to 30 cm long at their longest axis (Fig. 1 B, C).

#### Surgical technique

Once the oncological resection is concluded, the defect to be reconstructed is evaluated. The patient is placed in the lateral decubitus position and final marking of the skin island is performed, where the lower lateral border of the defect will become the anterior vertex of the skin island.

The skin island dissection proceeds until the plane of the *latissimus dorsi* muscle fascia is reached, where the superior portion of this flap is dissected and freed in the lateral-to-medial direction towards the thoracic spine apophyses and the lateral and inferior edge of the scapula until the



Figure 1. A-C: Anterior, lateral and posterior pre-surgical marking; D: Initial defect to be covered; E: Latissimus dorsi release and dissection; G: Lateral and posterior closure; H: Anterior defect closure.

axillary portion is reached. In this way, latissimus dorsi muscle vision is obtained from above the skin island. The same is performed on the inferior border of the island, only to take the inferior edge of the *latissimus dorsi*, with a muscle extension of between 5-7 cm. Once the entire extension of the latissimus dorsi is freed, its dissection is carried out from the medial-to-lateral direction, always under observation and caution only to dissect this muscle, especially respecting deep muscle planes. The upper portion of the chest lateral flap is then freed, exposing the lateral side, which enables the lifting of the flap to be carried out without a skin pocket, a usual problem of the traditional technique (Fig. 1 D).

The dissection is continued with insertions following until the axillary edge. The emergence of the thoracodorsal artery can be observed on the posterior side of the flap, which is where the dissection concludes, with this point being taken as an axis for rotation of the entire flap. The rotation movement is carried out in the posterior-to-anterior direction for skin coverage projection (Fig. 1 E, F).

The dorsal region reconstruction is characterized by the superior flap advancement following an inferior-medial tra-

Table 1.	Age.	tumor	characteristics	and	complications
----------	------	-------	-----------------	-----	---------------

	-		-			
	Age	Diagnosis	Stage	Breast	Tumor size	Complications
1	37	IDC	T3 N3 M0	R	12 x 15 cm	No
2	53	IDC	T4d N1 M0	L	12.5 cm	Hematoma
3	58	IDC	T4b N0 M0	R	16 x 12 cm	Medial third necrosis / infection
4	50	IDC	T4b N2 M0	L	17 cm	Partial dehiscence
5	37	IDC	T4d N3 M0	R	30 cm*	External third necrosis
6	43	IDC	T4d N3 M1	L	13.4 cm	No
7	46	MP	_	L	23 x 20 cm	No
8	43	MP	—	R	30 x 26 cm	No
9	36	MP	—	R	24 cm	Mov. limitation/ recurrence
10	33	IDC	T4b N3 M1	L	6 x 6 cm	No
11	29	MPC	T4d N2 Mo	R	8.5 cm	No
12	44	IDC	-	R	7.5 x 6.5 cm	No
13	39	MP		L	6 x 7 cm	No
14	54	IDC	T4d N3 M0	L	5.5 cm	No
15	37	IDC	T4b N2 M0	R	5.3 cm	No

\*Neoadjuvant chemotherapy, with final size of 7 x 5 cm + skin edema.

IDC: invasive ductal carcinoma; MP: malignant phyllodes; MPC: metaplastic carcinoma.

jectory, thus achieving a conventional result for the *latissimus dorsi* flap.

The patient is then rotated to the ventral decubitus position. Donor site closure is carried out by advancement and rotation of the superior flap in the anterior and inferior direction, trying to reduce the donor area and making the closure of the skin island territory, thus leaving a single result in continuity to the skin island, with a single drainage placed in the dorsal region and another by counter-aperture in the anterior region (Fig. 1 G, H).

# RESULTS

Over a five-year period, a total of 15 patients with advanced breast cancer or malignant phyllodes tumor (Fig. 2 and 3) were treated with radical and total mastectomy, respectively, with *latissimus dorsi* myocutaneous extended flap reconstruction. Mean age was 42.6 years (range: 29-58) (Table 1). Tumor dimension ranged from 5.3 to 30 cm, with a mean of 14.8 cm at the longest diameter (Table 1). Average follow-up was 15.8 months (range: 1-42) (Table 2).

The main indication for surgery was locally advanced breast cancer in 73% (11) of patients, with ductal infiltrating

Table 2.	Transoperative	hemorrhage,	surgical	time
and follov	v-up	-	-	

	Mean
Transoperative hemorrhage	653 cc (100-1,700)
Surgical time	255 min (180-330)
Follow-up	15.8 months (1-42)

carcinoma being the predominant diagnosis (66%), followed by malignant phyllodes tumor (26%) and, finally, by a case of metaplastic carcinoma.

In no case was it necessary for a rib cage resection to be performed, and during follow-up, a rate of local complications of 33% (5/15 patients) was found, with two patients experiencing more than one complication, mainly partial necrosis of the flap or dehiscence of some border. No total flap loss was reported. Most complications were minor and limited, with 60% being solved in the office (Table 1), and only one patient requiring reoperation (6.6%). All patients had adequate and satisfactory chest wall coverage, with no deaths being associated with the procedure.

# DISCUSSION AND CONCLUSIONS

The first reports on the prognosis of locally advanced carcinoma were described by Haagensen and Scout in 1940. Using modified radical mastectomy as single therapeutic measure, there was recurrence in 46% and five-year survival was only 6%<sup>25</sup>. In view of this experience, locally advanced carcinoma was initially classified as inoperable when there were complications such as extensive skin edema or satellite lesions, intercostal nodules, edema of the arm, supraclavicular metastasis or inflammatory cancer, ulceration, edema of the skin, fixation to pectoralis muscle, and bulky axillary adenopathy, which are poor prognosis factors and not necessarily un-resectability criteria. The role of reconstructive surgery in the treatment of locally advanced cancer is a topic of increasing interest owing to the development of innovative techniques that allow the surgeon to perform broad oncological resections, which previously would have been regarded as being unfeasible<sup>24</sup>.



Figure 2. Patient with stage IIIB infiltrating ductal carcinoma.



Figure 3. Patient with malignant phyllodes tumor. A: Pre-surgery; B: Post-surgery.

Myocutaneous, skin, or entirely muscle flaps have been shown to be acceptable alternatives for reconstruction in large defects<sup>18</sup>. The selection of the technique will depend on several factors including the defect size, status of the skin (peri- or post-radiotherapy), the surgeon's skills, and available resources (microvascular surgery, skin prostheses, vacuum system, etc.).

In general, initial surgical treatment in patients with locally advanced breast cancer is considered to be contraindicated. However, in the vast majority of our patients it is performed for palliative purposes, therefore usually being reserved to control local symptoms of advanced disease (pain, bleeding, ulceration, infection/necrosis). The latissimus dorsi extended flap has the advantage of being applicable to massive skin defects as large as 40 cm by replacing all cosmetic units of the breast regardless of the gland volume, which results in scarring free of skin bridges and without apparent physical sequels in the ranges of motion.

We are aware that a broad series of cases is required to appraise the sequels, complications, and ideal characteristics of the patients to be treated. With regard to the percentage of postsurgical complications, the vast majority was minor and limited, and probably associated either with clinical conditions or with comorbidities of our patients. In the literature we found complication rates similar to ours; for example, in 2004, Raymond carried out a 10-year review where he published a reoperation rate of 4%, associated with 16% of general complications (wound-healing delay, infections, or hematomas); on the other hand, Persichetti, et al. reports a complication rate of 22%, associated with 5% of reoperations<sup>18,26</sup>. This technique demands experience in the performance of myocutaneous flaps, but it is reproducible and is carried out in a single surgical intervention; it can be regarded as an excellent option in selected cases for partial or total reconstruction of chest wall large defects, for palliative or, in some cases, curative purposes. With this technique, covering resection areas of up to 40 cm is possible. We are convinced that the success of this technique depends on adequate patient selection and multidisciplinary, experienced treatment, coordinated between breast and plastic surgeons.

# DISCLOSURE OF INTEREST

The authors have no personal or financial relationships that might inappropriately influence (bias) on their work.

# REFERENCES

- Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69. Lancet. 2000;355:1822.
- Hortobagyi GN, Buzdar AU. Current status of adjuvant systemic therapy of primary breast cancer progress and controversy. CA Cancer J Clin. 1995;45:199-226.
- American Cancer Society. Surveillance and Health Policy Research. American Cancer Society. 2009. Available at: https://www.cancer.org/ content/dam/cancer-org/research/cancer-facts-and-statistics/annualcancer-facts-and-figures/2009/cancer-facts-and-figures-2009.pdf.
- Weir HK, Thun MJ, Hankey BF, et al. Annual report to the nation on the status of cancer, 1975-2000, featuring the uses of surveillance data for cancer prevention and control. J Natl Cancer Inst. 2003;95:1276-99.
- Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin. 2007;57:43-66.

- Palacio-Mejía LS, Lazcano-Ponce E, Allen-Leigh B, Hernández-Avila M. [Regional differences in breast and cervical cancer mortality in Mexico between 1979-2006]. Salud Publica Mex. 2009;51(Suppl 2):s208-19.
- Amin MB. Available at: https://cancerstaging.org/f. 2016 (Accessed January 2017).
- Edge SB. American Joint Committee on Cancer Staging Manual, 7th ed. 2010.
   Lee MC, Newman LA. Management of patients with locally advanced
- breast cancer. Surg Clin North Am. 2007;87:379-98. 10. Consenso Mexicano sobre Diagnóstico y Tratamiento del Cáncer Mama-
- rio. 2015; sexta revision. http://www.consensocancermamario.com/ documentos/RevistaGamo2015.pdf.
- Maffuz-Aziz A, Labastida-Almendaro S, Espejo-Fonseca A, Rodríguez-Cuevas S. [Clinical and pathological features of breast cancer in a population of Mexico]. Cir Cir. 2016. (Epub ahead of print).
- Sherwell-Cabello S, Maffuz-Aziz A, López-Hernández SN, Domínguez-Reyes CA, Labastida-Almendaro S, Rodríguez-Cuevas S. Young age: The most significant factor contributing to poorer prognosis in Mexican women with breast cancer. J Cancer Biol Res. 2015;3:1066.
- Robles-Castillo J, Ruvalcaba-Limón E, Maffuz A, Rodríguez-Cuevas S. [Breast cancer in Mexican women under 40]. Ginecol Obstet Mex. 2011;79:482-8.
- Olivotto IA, Chua B, Allan SJ, Speers CH, Chia S, Ragaz J. Long-term survival of patients with supraclavicular metastases at diagnosis of breast cancer. J Clin Oncol. 2003;21:851-4.
- Samuels L, Granick MS, Ramasastry S, Solomon MP, Hurwitz D. Reconstruction of radiation-induced chest wall lesions. Ann Plast Surg. 1993;31:399-405.
- Rouanet P, Fabre JM, Tica V, Anaf V, Jozwick M, Pujol H.. Chest wall reconstruction for radionecrosis after breast carcinoma therapy. Ann Plast Surg. 1995;34:465-70.

- Beahm EK, Chang DW. Chest wall reconstruction and advanced disease. Semin Plast Surg. 2004;18:117-29.
- Persichetti P, Tenna S, Cagli B, Scuderi N. Extended cutaneous 'thoracoabdominal' flap for large chest wall reconstruction. Ann Plast Surg. 2006;57:177-83.
- Tai Y, Hasegawa H. A transverse abdominal flap for reconstruction after radical operations for recurrent breast cancer. Plast Reconstr Surg. 1974;53:52-4.
- Brown RG, Vasconez LO, Jurkiewicz MJ. Transverse abdominal flaps and the deep epigastric arcade. Plast Reconstr Surg. 1975;55:416-21.
- Larson DL, McMurtrey MJ. Musculocutaneous flap reconstruction of chest-wall defects: an experience with 50 patients. Plast Reconstr Surg. 1984;73:734-40.
- Sodha NR, Azoury SC, Sciortino C, Sacks JM, Yang SC. The use of acellular dermal matrices in chest wall reconstruction. Plast Reconstr Surg. 2012;130(Suppl 2):175-825.
- Arnold PG, Pairolero PC. Chest wall reconstruction: an account of 500 consecutive patients. Plast Reconstr Surg. 1996;98:804-10.
- Munhoz AM, Montag E, Arruda E. Immediate locally advanced breast cancer and chest wall reconstruction: surgical planning and reconstruction strategies with extended V-Y latissimus dorsi myocutaneous flap. Plast Reconstr Surg. 2011;127:2186.
- Haagensen CD, Stout AP. Carcinoma of the breast II. Criteria of operabitity. Ann Surg. 1943;118:1032-51.
- Chang RR, Mehrara BJ, Hu QY, Disa JJ, Cordeiro PG. Reconstruction of complex oncologic chest wall defects a 10 years experience. Ann Plast Surg. 2004;52:471-9.
- Jay R, Morrow M, Osborne CK. Diseases of the Breast. 4th ed. Philadelphia, PA: Lippincott Williams and Wilkins. 2014.



SOCIEDAD MEXICANA DE ONCOLOGÍA, A.C. GACETA MEXICANA DE ONCOLOGÍA WWW.gamo-smeo.com

# ORIGINAL ARTICLE



# Prognostic Factors in Patients Diagnosed with High Grade Glioma Managed with Radiotherapy: Experience at the Federico Gómez Children's Hospital of Mexico

María Fátima Chilaca-Rosas<sup>1,2,\*</sup>, Heynar de Jesús Pérez-Villanueva<sup>2,3</sup>, Noé Trinidad-Hernández<sup>2,4</sup>, Juan Carlos Heredia-Gutiérrez<sup>5</sup> and Héctor Urueta-Cuéllar<sup>6</sup>

<sup>1</sup>Department of Pediatric Radiotherapy, Oncology Hospital, Centro Médico Nacional Siglo XXI; <sup>2</sup>Department of Pediatric Radiotherapy, Hospital Infantil de México Federico Gómez; <sup>3</sup>Radiotherapy Department, Hospital General de México Eduardo Liceaga; <sup>4</sup>Department of Radiotherapy Physics, Oncology Hospital, Centro Médico Nacional Siglo XXI; <sup>5</sup>Radiotherapy Department, Oncology Hospital, Centro Médico Nacional Siglo XXI; <sup>6</sup>Department of Genetics, Hospital General de México Eduardo Liceaga; Mexico City, Mexico

Received for publication: 5 January 2016; accepted for publication: 25 February 2017 Available online: 10 July 2017

# **KEYWORDS**

High-grade glioma; Surgical resection; Conformal radiotherapy; Pediatrics Abstract Introduction: High-grade gliomas account for 15-20% of intracranial tumors in the pediatric population, usually with poor prognosis for overall survival. Objective: To identify prognostic factors for overall survival and local control in patients diagnosed with intracranial high-grade gliomas managed with conformal radiotherapy. Patients and methodology: This retrospective study assessed all high-grade glioma-diagnosed patients treated with radiotherapy at the Federico Gómez Children's Hospital over the period 2008-2013 by means of a review of medical records, imaging files, and treatment plans. Results: The analyzed patients (n = 18) had a median age of five years. The most common localization was infratentorial. Histologies found were glioblastoma multiforme and anaplastic astrocytoma. Of the analyzed patients, 44.4% received surgical management owing to the lesion localization and their performance status. All patients received radiotherapy with > 54 Gy total dose with or without chemotherapy. Local control rate was 94.4% and median overall survival was 13 months. With regard to surgical management for gross tumor resection, subtotal tumor resection, and no resection, five-year overall survival was 100, 50, and 36%, respectively (p = 0.04). The patients showed overall survival improvement with radiotherapy total dose > 54 Gy and standard fractioning. Conclusion: In the present study, surgical gross resection and management with standard external beam radiotherapy at doses > 54 Gy were found to be predictive factors for overall survival in pediatric patients diagnosed with intracranial highgrade gliomas. (creativecommons.org/licenses/by-nc-nd/4.0/).

\*E-mail for correspondence: fatychro@hotmail.com (M.F. Chilaca-Rosas)

http://dx.doi.org/10.24875/j.gamo.17000004

1665-9201 / © 2017 Sociedad Mexicana de Oncología. Publicado por Permanyer México. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

# INTRODUCTION

Central nervous system tumors are at third place in incidence among all solid tumors, with a rate of 29.7 per million at the pediatric age. Astrocytomas are the most common glioma subgroup, and involve 40-50% of intracranial tumors in the pediatric population. The high-grade group is comprised by anaplastic astrocytoma (with or without oligodendroglial component) and glioblastoma multiforme (GBM)<sup>1</sup>. Highgrade astrocytomas or gliomas are infrequent in the pediatric population, accounting for 15-20% of intracranial tumors.

The etiology of high-grade glioma (HGG) has not yet been fully determined, but factors associated to its carcinogenesis are known, including exposure to ionizing radiation, as well as its genetic, molecular, histological, clinical, and therapeutic characteristics, which even have been shown to be prognostic factors for disease-free survival (DFS) and overall survival (OS)<sup>2-4</sup>.

The HGG clinical features are generally related to its localization, as in the case of the supratentorial area, where usually it can cause compression or obstruction of the ventricular system and produce hydrocephalus and usually symptoms consistent with intracranial hypertension such as headache, nausea, and vomiting. The presence of dysphasia, hemiparesis, and tonic-clonic seizures with focalization according to the primary site has been correlated with the degree of rapid progression, which confers poor prognosis in terms of OS. In the case of infratentorial localization, more related to posterior fossa involvement, cerebellar mutism, and positional vertigo involvement or dysfunction, there can also be signs and symptoms associated with hydrocephalus and intracranial hypertension<sup>4,5</sup>. The study technique with the highest diagnostic sensitivity and specificity is contrasted magnetic resonance imaging (MRI), where adequate assessment should be with at least T1-weighted sequences with and without contrast for lesions with heterogeneous solid component and irregular borders, with enhancement after the contrast medium is applied, as well as centrally predominating areas of necrosis and calcification. To assess edema, T2/FLAIR-weighted reconstruction is used. In case the resource of multi-parametric MRI is available, functional MRI should be performed with spectroscopy, perfusion, and diffusion for better diagnosis of tumor activity by imaging<sup>6-8</sup>.

Initial standard treatment for HGG is multimodal, with extensive surgery or gross total resection being the cornerstone at any age. In children older than three years, it will be supplemented with standard radiotherapy adjuvant management at doses not higher than 60 Gy and/or chemotherapy<sup>8-12</sup>. Late toxicity, such as neurocognitive or neuroendocrine alterations and vasculopathy, should be evaluated when the treatments are offered<sup>13</sup>.

The role of adjuvant chemotherapy remains controversial in patients older than three years since its use has been suggested to improve the prognosis in terms of DFS, but not of OS, or it increases it modestly, as assessed in reports of the Cancer Pediatric Group with the scheme based on lomustine, vincristine, and prednisone<sup>14</sup>.

However, there is conflicting evidence in pediatric patients, with temozolomide management concomitant with radiotherapy having been assessed in pediatric patients with no benefit in terms of DFS or  $OS^{15-17}$ , as well as in patients with recurrent HGG on the prolonged scheme of 90 mg/m<sup>2</sup> for 21 days for four weeks with no OS benefit in the phase II trial by Nicholson<sup>18</sup>, et al. in contrast with trials where an impact on local control (LC), DFS, and OS is reported, as in the study by Stupp, et al.<sup>19</sup>, although in this trial most patients were adults.

In patients younger than three years, after surgical treatment, radiotherapy will be reserved only for necessary cases such as disease progression and inadequate control with chemotherapy, owing to the late morbidity radiotherapy can confer. In case postponing radiotherapy is possible, chemotherapy management should be implemented with schemes based on lomustine, vincristine, prednisone, ifosfamide, carboplatin, and etoposide<sup>20,21</sup>.

The main purpose of the present study was to assess prognostic factors and their impact in terms of LC and OS in HGG-diagnosed patients on multimodal treatment at the Federico Gómez Children's Hospital.

# MAIN OBJECTIVE

To assess prognostic factors in terms of OS and LC in patients diagnosed with HGG managed with external beam radiotherapy at the Federico Gómez Children's Hospital.

# SECONDARY OBJECTIVES

To identify prognostic factors related to characteristics of the neoplasm in terms of localization, and with regard to the multimodal management and their impact on LC and OS.

## MATERIAL AND METHODS

The present observational, retrospective study assessed all patients diagnosed with HGG over the period from 2008 through 2013 at the Department of Pediatric Radiotherapy of the Federico Gómez Children's Hospital. Analyzed patients were those who met the following criteria:

Inclusion criteria:

- 0-17-year old patients.
- Patients with histological and/or imaging diagnosis of HGG (in case of brainstem localization), regardless of localization.
- Patients with a 60-100% Lansky score.
- Patients diagnosed with HGG who have received management with external beam radiotherapy and/or chemotherapy with ifosfamide/carboplatin/etoposide scheme and/or temozolomide in concomitant and/or adjuvant form.

Exclusion criteria:

- Patients with concurrent malignancy or history thereof within the previous five years (except for benign or genetic syndrome-related lesions).
- Patients with medically unstable conditions to receive external radiotherapy management (hemodynamically, neurologically, metabolically, or infectologically).



Figure 1. Distribution by percentage of patients with high-grade glioma by state in the country.

# Techniques and procedures

Patients previously assessed by the neurosurgery department of the Federico Gómez Children's Hospital and hospitals with an agreement therewith, with a diagnosis consistent with HGG by imaging or with histological corroboration by previous surgical manipulation.

# Surgical treatment

Surgical procedures contemplated by the referral department in some patients were gross total resection or maximal resection (> 90%), subtotal resection (< 90%), and ventricular bypass drainage system placement according to each patient's clinical context. The extension of the surgery was assessed by tomography or MRI 24-72 hours postoperatively.

# Radiotherapy treatment

External beam radiotherapy treatment was provided with a linear accelerator (Varian System®), with 6 MV energy and Eclipse® planning system, version 7.3; in all cases, based on 3D conformal technique with coplanar and non-coplanar fields, with doses in the biological effect dose 50-60 Gy range. The GBM cases were defined as gross tumor volume (GTV) = tumor evidenced by imaging or contrast-enhanced surgical bed by MRI (previously fused), clinical target volume (CTV) 1 = GTV + FLAIR/T2 sequence-characterized perilesional edema + 1 cm margin, planning treatment volume (PTV) 1 = CTV1 + 3-5 mm; CTV2 = GTV + 1 cm margin, PTV2 = CTV2 + 3-5 mm. In the anaplastic astrocytoma cases and brainstem localization, GTV = tumor evidenced by contrast-enhanced MRI, CTV = GTV + 1 cm, PTV = CTV + 3-5 mm.

Fractioning for patients was mostly conventionally assigned and only in two cases was modified management decided with hypofractioning, due to uncertainty on patient neurological stability but, after improvement, dose escalation was contemplated, and the second phase was delivered with standard fractioning for a 60 Gy biological effect dose.

# Chemotherapy treatment

Chemotherapeutical management was administered based on the following scheme:

- Ifosfamide: 2 g/m<sup>2</sup>/day, for one day;
- Carboplatin 30 mg/m<sup>2</sup>, for three days;

- Etoposide: 100 mg/m<sup>2</sup>, for two days
- Temozolomide at 100 mg/m<sup>2</sup> for five days at each cycle for at least six cycles.

In some hospitals with an agreement with our institution, chemotherapeutic management was not offered.

# Surveillance

The surveillance scheme includes three-monthly skull contrasted MRI over the first year and every four months during the second year, every semester in the third year, and in both fourth and fifth year, annually or before this period for clinically necessary reason.

# Data analysis

The statistical analysis was carried out using the GraphPad Prism<sup>®</sup> statistical package, version 6.0. Descriptive statistics was used to determine the median by population distribution type. To calculate and obtain the OS, the log-rank assessment was used, with different Gehan-Breslow-Wilcoxon tests. With regard to HGG by state in the country, as well as to the neoplasm intracranial localization distribution, a distribution graph determination was performed.

# RESULTS

A total of 102 patients diagnosed with glioma, out of which 18 patients (17.6%) had HGG, were assessed by the Radiotherapy Department of the Federico Gómez Children's Hospital of Mexico over the period from 2008 through 2103. Most assessed patients came from Mexico City (then Distrito Federal) and the State of Mexico (Fig. 1).

Median age of the patients diagnosed with HGG-related intracranial lesions was five years, with no gender being predominant (Table 1), and the most common localization was infratentorial, specifically in the brainstem in 10 patients (55.6%). The reported histologies of the patients were anaplastic astrocytoma and GBM.

With regard to the management of patients amenable to surgical treatment, eight patients (44.4%) underwent surgery, with the procedure being gross tumor resection in four subjects (22.2%). Those patients who were not offered initial surgical management owing to localization or any other limitation were offered external radiotherapy management.

All patients (n = 18) received external beam radiotherapy and/or concomitant or adjuvant chemotherapy based on the ifosfamide/carboplatin/etoposide and/or temozolomide scheme. In some patients, external radiotherapy had a protracted prolongation owing to concomitant management-associated comorbidities, as well as to increased intracranial hypertension, which was improved with ventricular bypass valve changes.

# Local control analysis

In most patients, adherence to post-treatment follow-up was not adequate, mainly owing to economic reasons, which limited the attainment of control imaging studies, with only initial local control data being obtained, but not an ade-

Table 1. Patient and disease characteristics

Characteristics	Total = 18 patients (100%)
Age	5-year median (3-15 years)
Gender (male:female) Genetic alterations or syndromes: — Type 1 neurofibromatosis	1:1.3 1 (5.5%)
Localization: — Supratentorial (parietal and temporal lobes) — Infratentorial (brainstem and posterior fossa)	5 (27.8%) 13 (72.2%)
Histology (suggested by imaging and pathology): — Anaplastic astrocytoma — Glioblastoma multiforme	16 (88.9%) 2 (11.1%)
Clinical findings: – Headache – Cranial nerve alteration – Ataxic gait – Seizures	7 (39%) 7 (39%) 6 (33.3%) 6 (33.3%)
Surgical management: – Gross tumor resection (95-100%) – Subtotal resection (< 95%) – None	4 (22.2%) 4 (22.2%) 10 (55.6%)
Management with external radiotherapy (fractioning): — Modified — Standard	2 (11.1%) 16 (88.9%)
Radiotherapy total dose: — Lower than 54 Gy — Equal to or greater than 54 Gy	2 (11.1%) 16 (88.9%)
Chemotherapy: – ICE scheme – Temozolomide scheme – ICE with temozolomide scheme – None	1 (5.5%) 5 (27.8%) 10 (55.6%) 2 (11.1%)

Gy: Gray; ICE: Ifosfamide-Carboplatin-Etoposide-based chemotherapy scheme.

quate follow-up thereof in order to be able to objectively establish the disease-free interval for all analyzed patients.

In patients where control follow-up imaging data could be collected after the completion of the external radiotherapy treatment with 54-60 Gy doses, partial response was observed at 6-8 months in 50%, with subsequent stability of the disease status until death, and only in three cases was a complete response obtained at 15 months of treatment completion and, hence, a DFS of 100% at three years.

#### Overall survival analysis

Information on survival could be obtained from all patients, and therefore the analysis was performed, which yielded a five-year OS of 37%, with a median of 13 months (Fig. 2).

Subsequently, different patient and neoplasm-inherent factors were analyzed in order to assess their effect on OS.

No correlation of OS with age was made because in the series there were no patients younger than three years, neither was it made with molecular alterations because these were not assessed.

The factors that were observed to have an influence on OS in this case series were: surgical intervention, external radiation therapy dose, and radiotherapy treatment type of fractioning.

With regard to the surgical procedure, an 18-month OS of 100 vs. 50 vs. 36% was obtained for gross total resection, subtotal resection, and no surgical intervention, respectively (Fig. 3). Overall survival was increased with external radiotherapy doses higher than 54 Gy, with median survival of 19 vs. 7 months with lower doses, p = 0.0002 (Fig. 4 A and 4 B).

In the assessment of the fractioning type, an improvement in OS was found with standard fractioning, with a median of 20 vs. 10 months; p = 0.02 (Fig. 5).



Figure 2. Overall survival analysis graph by means of the log-rank test (Mantel Cox test).



Figure 4 A. Overall survival graph according to 3D conformational external radiotherapy total dose by log-rank analysis (Gehan-Breslow-Wilcoxon test), with statistical significance in both groups (p = 0.0002).



Figure 5. Overall survival graph according to 3D conformational external radiotherapy type of fractioning by log-rank analysis (Mantel-Cox test).



Figure 3. Overall survival graph according to surgical intervention by log-rank analysis, p = 0.04 (trend test).



Figure 4 B. Overall survival graph according to different 3D conformational external radiotherapy total doses by log-rank analysis (Gehan-Breslow-Wilcoxon test).

Factors such as tumor histology and management with chemotherapy were also analyzed, but none of these factors was found to impact on OS.

# DISCUSSION

In the present study, the prevalence of HGG was assessed to be 17% in our pediatric population, which is similar to figures reported in the literature<sup>13</sup>. Median age of the patients was five years, with no gender being predominantly affected and with infratentorial localization (specifically in the brainstem) being more common. Brainstem-located gliomas (55.6%) did not receive any surgical intervention or biopsy because these were diffuse lesions, with this being highly relevant since, by not being able to determine the glioma histological characteristics, there will always be higher uncertainty about the tumor behavior, as has been described in the world literature<sup>22</sup>. With regard to the determination of molecular and genetic prognostic factors (mutations, chromosomal alterations, or genetic syndromes) that have been reported in the world literature to have an impact on  $OS^{2,23}$ , in the present study it was not assessed because no molecular determinations or profiles could be carried out in our Institution, and only in one patient (5.6%) was the presence of type 1 neurofibromatosis syndrome established by clinical examination.

Surgical management with gross tumor resection was only possible in 22.2% and subtotal resection in 22.2%, and no surgical intervention was carried out in the brainstem-located cases. After surgical management, or in patients who were not candidates for it, external beam radiotherapy was immediately offered, mostly with conventional fractioning, with clinical improvement being observed at the end of radiotherapy treatment with an improvement in performance status. Patients were treated with a median dose of 54 Gy, with this dose being predominant owing to large volumes and at-risk organs restriction. External radiotherapy administration was concomitant and adjuvant with temozolomide, except in two cases (11.1%) where no chemotherapy was offered.

Local control assessment at follow-up could not be adequately determined in this study due to the failure to obtain imaging studies, as already commented in the results section, which impacted on the progression-free interval assessment. However, in patients where it could be assessed with post-treatment control studies, stable disease was observed at six months and, after eight months, there was partial response of at least 50%, and complete response in three cases at 15 months; in the remaining patients, stable disease was observed for up to 12 months until progression and death.

The patients who achieved a complete response at 15 months had a DFI of three years. It should be noted that these patients underwent at least subtotal resection and management with external beam radiotherapy at doses higher than 55 Gy, with adjuvant chemotherapy for up to six cycles and, in one case, in spite of the corroborated histological lineage being GBM, with subtotal resection and external radiotherapy with concomitant temozolomide and adjuvant ifosfamide/carboplatin/etoposide scheme, a complete response was achieved with a DFI of 42 months.

With regard to the 37% OS obtained in the present study at five years, this is slightly lower than that reported in the literature, probably owing to the high percentage of patients with no surgical intervention due to brainstem localization, although in the analysis of factors in the present study, the tumor localization factor did not statistically significantly impact on  $OS^{21}$ .

The factors that influenced OS in this study included the gross tumor resection, with its influence already being apparent at 18 months, with an important decrease of 50% when gross tumor resection was not achieved and a worse outcome when no surgical intervention was performed.

Another important factor that was assessed in the present study was external beam radiotherapy management, with doses higher than 54 Gy and standard fractioning favorably impacting on OS. Although the literature has only reported that the suggested dose is 55.8 Gy<sup>22</sup>, a trend towards the dependence of OS on higher doses was observed in this study, as well as an OS improvement with standard fractioning, as previously proposed by authors such as Chan, et al. in  $2002^{24}$ .

Although tumor histology has been reported to impact on OS by reducing it by 50% when GBM is compared with anaplastic astrocytoma, in this case series no such trend was observed<sup>11</sup>, probably owing to the fact that GBM-diagnosed patients were surgically intervened with at least subtotal resection and received external radiotherapy management at a total dose of 60 Gy with standard fractioning and six cycles of concomitant chemotherapy.

Although chemotherapy did not statistically significantly modify OS as a single factor in this group of patients, it had at least an effect on disease stability, as has been observed in the literature<sup>23</sup>.

# CONCLUSION

In the present study, gross tumor resection and subsequent adjuvant management with external beam radiotherapy at a dose higher than 54 Gy and up to 60 Gy with standard fractioning were found to be the main overall survival prognostic factors in pediatric patients diagnosed with intracranial high-grade glioma.

# REFERENCES

- Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO Classification of Tumours of the Central Nervous System. Acta Neuropathologica. 2007;114:97-109.
- Pollack IF, Finkelstein SD, Woods J, et al. Expression of p53 and prognosis in children with malignant gliomas. N Eng J Med. 2002;346:420.
- Liu W, James CD, Frederick L, Alderete BE, Jenkins RB. PTEN/MMAC1 mutations and EGFR amplification in glioblastomas. Cancer Res. 1997;57:5254
- Rickert CH, Sträter R, Kaatsch P, et al. Pediatric high grade astrocytomas show chromosomal imbalances distinct from adult cases. Am J Pathol. 2001;158:1525-32.
- Mehta V, Chapman A, McNeely PD, Walling S, Howes WJ. Latency between symptom onset and diagnosis of pediatric brain tumors: an Eastern Canadian geographic study. Neurosurgery. 2002;51:365-72.
- Steffen-Smith EA, Shih JH, Hipp SJ, Bent R, Warren KE. Proton magnetic resonance spectroscopy predicts survival in children with diffuse intrinsic pontine glioma. J Neurooncol. 2011;105:365-73.
- Duffner PK. Diagnosis of brain tumors in children. Expert Rev Neurother. 2007;7:875-85.
- Cage TA, Mueller S, Haas-Kogan D, Gupta N. High grade gliomas in children. Neurosurg Clin North Am. 2012;23:515-23.
- Fulton DS, Urtasun RC, Scott-Brown I, et al. Increasing radiation dose intensity using hyperfractionation in patients with malignant glioma. Final report of a prospective phase I-II dose response study. J Neurooncol. 1992;14:63.
- Packer RJ, Boyett JM, Zimmerman RA, et al. Hyperfractionated radiation therapy (72 Gy) for children with brain stem gliomas. A Childrens Cancer Group Phase I/II Trial. Cancer. 1993;72:1414.
- Wisoff JH, Boyett JM, Berger MS, et al. Current neurosurgical management and the impact of the extent of resection in the treatment of malignant gliomas of childhood: a report of the Children's Cancer Group trial no. CCG-945. J Neurosurg. 1998;89:52-9.
- Hyder DJ, Sung L, Pollack IF, et al. Anaplastic mixed gliomas and anaplastic oligodendroglioma in children: results from the CCG 945 experience. J Neurooncol. 2007;83:1-8.
- Gupta N. Pediatric CNS Tumors. 2nd Edition. Berlín, Heidelberg: Springer; 2010;37-43.
- Sposto R, Ertel IJ, Jenkin RD, et al. The effectiveness of chemotherapy for treatment of high grade astrocytoma in children: results of a randomized trial. A report from the Childrens Cancer Study Group. J Neurooncol. 1989;7:165.

- Cohen KJ, Pollack IF, Zhou T, et al. Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. Neuro Oncol. 2011;13:317.
- Lashford LS, Thiesse P, Jouvet A, et al. Temozolomide in malignant gliomas of childhood: a United Kingdom Children's Cancer Study Group and French Society for Pediatric Oncology Intergroup Study. J Clin Oncol. 2002;20:4684-91.
- Estlin EJ, Lashford L, Ablett S, et al. Phase I study of temozolomide in paediatric patients with advanced cancer. United Kingdom Children's Cancer Study Group. Br J Cancer. 1998;78(5):652-61.
- Nicholson HS, Kretschmar CS, Krailo M, et al. Phase 2 study of temozolomide in children and adolescents with recurrent central nervous system tumors: a report from the Children's Oncology Group. Cancer. 2007;110:1542.
- 19. Stupp R, Dietrich PY, Ostermann Kraljevic S, et al. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. J Clin Oncol. 2002;20:1375.

- 20. Finlay JL, Boyett JM, Yates AJ, et al. Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen. Childrens Cancer Group. J Clin Oncol. 1995;13:112-23.
- Wolff JE, Gnekow AK, Kortmann RD, et al. Preradiation chemotherapy for pediatric patients with highgrade glioma. Cancer. 2002;94: 264-71.
- 22. Packer RJ. Primary central nervous system tumors in children. Curr Treat Options Neurol. 1999;1:395-408.
- Sung T, Miller DC, Hayes RL, Alonso M, Yee H, Newcomb EW. Preferential inactivation of the p53 tumor suppressor pathway and lack of EGFR amplification distinguish de novo high grade pediatric astrocytomas from de novo adult astrocytomas. Brain Pathol. 2000;10: 249-59.
- Chan JL, Lee SW, Fraass BA, et al. Survival and failure patterns of high-grade gliomas after three-dimensional conformal radiotherapy. J Clin Oncol. 2002;20:1635-42.



SOCIEDAD MEXICANA DE ONCOLOGÍA, A.C. GACETA MEXICANA DE ONCOLOGÍA WWW.gamo-smeo.com



# ORIGINAL ARTICLE

# Cost-Benefit Study of Febrile Neutropenia Prophylactic Treatment with Pegfilgrastim vs. Filgrastim in Pediatric Patients with Solid Tumors

Norma Araceli López-Facundo<sup>1,\*</sup>, Ma. Guadalupe Valois-Escamilla<sup>2</sup>, Isidoro Tejocote-Romero<sup>1</sup>, Cecilia Rodríguez-Castillejos<sup>3</sup> and Yanet Jaimes-García<sup>1</sup>

<sup>1</sup>Department of Pediatric Oncology, <sup>2</sup>Pediatrics Department and <sup>3</sup>Department of Pediatric Hematology; Hospital Materno-Infantil, ISSEMYM, Toluca, Estado de México, Mexico

Received for publication: 6 December 2016; accepted for publication: 25 February 2017 Available online: 10 July 2017

## **KEYWORDS**

Cost-benefit; Pegfilgrastim; Febrile neutropenia Abstract Background: Febrile neutropenia is one of the main complications in cancer patients that exponentially increases treatment costs. Pegfilgrastim is a pegylated form of filgrastim, and it might reduce the severity and duration of febrile neutropenia, as well as costs. **Objective:** To analyze the cost-benefit ratio of febrile neutropenia prophylactic treatment with pegfilgrastim vs. filgrastim in pediatric patients with solid tumors. Methods: A cost-benefit study was carried out, where complete medical records of pediatric patients with solid tumors and febrile neutropenia who received prophylactic treatment with pegfilgrastim vs. filgrastim were analyzed. Clinical-demographic variables, febrile neutropenia events, and days of hospital stay were considered, as well as related complications and global related cost, looking for differences by means of Student's t-test and the chi-square test. Results: Twenty-six patients with a total of 106 chemotherapy courses were included. Fourteen patients (52.8%) were administered filgrastim and 12 patients (46.1%) received pegfilgrastim. There were 57.6% of males. Mean hospital days of stay and costs were significantly higher in the filgrastim versus the pegfilgrastim group (p < 0.001). Conclusion: The use of pegfilgrastim reduced the number of neutropenia and fever events, days of hospital stay, and costs by up to 30%. (creativecommons.org/ licenses/by-nc-nd/4.0/).

\*E-mail for correspondence: oncouaem2009@hotmail.com (N.A. López-Facundo)

http://dx.doi.org/10.24875/j.gamo.17000005

1665-9201 / © 2017 Sociedad Mexicana de Oncología. Publicado por Permanyer México. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

# INTRODUCTION

Costs associated with febrile neutropenia (FN)-related hospitalization significantly add to the direct medical costs of cancer treatment, and entail a heavy financial burden on these patients' global care<sup>1-4</sup>. Individuals with FN can be treated as in- or outpatients according to the risk for complications<sup>5</sup>. Multiple cost-utility models have been developed in order to compare the economic effects of different therapeutic alternatives. Randomized trials with sargramostim, filgrastim, and pegfilgrastim have been reported, which have shown significantly less FN events and FN-related hospital-stay days and, therefore, lower costs related to these events<sup>6</sup>. In other pharmacoeconomic studies conducted in the USA, a cost decrease has been observed with the use of primary prophylaxis in patients receiving chemotherapy. Among the granulocyte colony-stimulating factor (G-CSF) drugs, pegfilgrastim appears to be superior to filgrastim in terms of cost minimization, and primary prophylaxis seems to be less expensive than secondary prophylaxis. A decrease in the risk of infection-related mortality has been observed, as well as the benefit of being able to maintain the chemotherapy dose intensity with the support of G-CSF agents<sup>7-10</sup>. A cost-utility model based on usual clinical practice for the treatment of FN with immediate hospitalization or ambulatory treatment, developed in the USA, provides robust evidence indicating that pegfilgrastim is not only costeffective but it also generates cost savings in clinical areas by reducing mean hospitalization-day costs estimated in patients who survived a FN event with regard to those who died. At baseline conditions, pegfilgrastim is superior to filgrastim and other G-CSF agents, with expected costs and effectiveness of US\$ 4,203 and 12,361 gualityadjusted life-days (QALD) in case of no G-CSF use, US\$ 3,058 and 12,967 QALDs with pegfilgrastim, and US\$ 5,655 and 12,698 QALDs with the use of filgrastim, which indicates that pegfilgrastim prophylactic administration produces both clinical and economic benefits<sup>3-12</sup>. In the UK, Germany, and Japan, studies with G-CSF agents have been carried out in breast cancer, with pegfilgrastim-associated FN absolute risk being estimated to be 5.5% lower than with 10 days on filgrastim (7 vs. 12.5%), and 10.5% lower than with six days on filgrastim (7 vs. 17.5%). A very elevated incremental cost-effectiveness ratio per life-year gained was shown, with an up to Euros 2,229 saving being found, and an adjusted gain of 0.039 guality-adjusted life-years (QALY) with the use of primary prophylaxis with pegfilgrastim<sup>13-16</sup>. Cost-efficacy studies of G-CSF agents such as biosimilar filgrastim and pegfilgrastim have been carried out in European countries<sup>17</sup>. Febrile neutropenia prophylaxis or treatment with the biosimilar drug is cost-effective in all possible treatment scenarios with regard to filgrastim and pegfilgrastim<sup>18-30</sup>.

There are few pediatric clinical trials to validate pegfilgrastim safety and effectiveness in children. However, those already reported suggest good tolerance and safety, with few side effects<sup>31,32</sup>.

The purpose of the present study was to assess the cost-benefit ratio of FN prophylaxis with pegfilgrastim vs. filgrastim in pediatric patients with solid tumors.

## MATERIAL AND METHODS

Medical records of pediatric patients with solid tumors who received at least four courses of myeloablative chemotherapy were included in a cost-benefit study carried out at the Pediatric Oncology Unit of the Mother-Child Hospital of the Institute of Social Security of the State of Mexico and Municipalities. The patients had to have received a single dose of pegfilgrastim (Neulastim®) of 100 mcg/kg at day 6 and were compared with a historical cohort of patients who received filgrastim (Inmunef® or Neupogen®) at 5 mcg/kg/day from day 6 to 15 during the period of December 2010 through July 2013. Courses where the patients had received radiotherapy simultaneous to chemotherapy or one month prior to chemotherapy were excluded. Clinical-demographic variables such as age, gender, type of tumor, administered chemotherapy scheme, number of FN events requiring hospitalization (with neutropenia being regarded as an absolute neutrophil count < 1,500 and fever as a temperature > 38.3 in two occasions or a fever peak > 39 degrees, according to the WHO), blood count at hospital admission, type of infection, presence of FN-related complications, number of hospital days of stay, as well as global costs associated with these events, were assessed. The costs of bed-day, medications including filgrastim extra doses, laboratory and imaging studies, among others, were considered.

The costs were provided and crosschecked by the Accountability Department of the Hospital based on figures published in the Government Gazette. Data were analyzed using the SPSS software, version 17. Descriptive statistics was used with central tendency and dispersion measures, as well as Student's *t*-test and the chi-square test to look for differences in both groups. In addition, hospitalization risk was determined by means of bivariate analysis.

The present study was approved by the Research Ethics Committee of the Hospital.

#### RESULTS

The medical records of 26 patients with a total of 106 chemotherapy courses were thoroughly analyzed. There were 57.6% males and 42.3% females in the sample, with an average age at first chemotherapy course of 91.4  $\pm$  66.1 months (9-192 months). The main tumors included in this study are described in table 1. Of the 106 chemotherapy courses, pegfilgrastim prophylaxis was administered 52 times in 12 patients (46.1%).

The main chemotherapies used in these patients are described in table 1. The following doses were administered:

- ifosfamide 1.8 g/m<sup>2</sup> SC d1-5, carboplatin 450 mg/m<sup>2</sup>
   SC d1, etoposide 100 mg/m<sup>2</sup> SC d1-5 (ICE);
- vincristine 2 mg/m<sup>2</sup> SC d1, ifosfamide 1.8 g/m<sup>2</sup> SC d1-5, actinomycin D 15 mcg/kg d1-5, etoposide 100 mg/m<sup>2</sup> SC d1-5 (VAI-VIE);
- vincristine 2 mg/m<sup>2</sup> d1, Adriamycin 35 mg/m<sup>2</sup> SC d1-2, cyclophosphamide 2.1 g/m<sup>2</sup> SC d1-2 (VAC).

Febrile neutropenia requiring hospitalization occurred in 35 occasions in 9/53 chemotherapy courses receiving prophylactic pegfilgrastim vs. 26/53 courses prophylactically treated with filgrastim. In the bivariate analysis for hospitalization risk in pegfilgrastim-treated patients, an overall risk

	Filgrastim (n = 14)	Pegfilgrastim (n = 12)
Age in months	Mean 97 (12-204)	Mean 112 (12-192)
Gender:		
— Male	8	7
– Female	6	5
Diagnosis:		
— Rhabdomyosarcoma	3	3
<ul> <li>Germ cell tumors</li> </ul>	3	2
— Soft tissue sarcoma	2	2
— Wilms tumor	1	0
<ul> <li>Neuroblastoma</li> </ul>	2	2
— Other	3	3
Type of chemotherapy*:	N53	N53
— ICE	25	27
- VAI-VIE	24	25
- VAC	4	1

Table 1. Characteristics of pediatric patients with solidtumors who received febrile neutropenia prophylaxis withfilgrastim vs. pegfilgrastim

\*Number of chemotherapy courses.

ICE: ifosfamide/etoposide with or without carboplatin; VAC:

vincristine, actinomycin, cyclophosphamide; VAI: vincristine,

actinomycin, ifosfamide; VIE: vincristine, ifosfamide, etoposide.

of 0.21 was obtained (95% CI: 0.08-0.5; p = 0.01), indicating that the use of pegfilgrastim significantly decreased the number of hospitalizations. Hospitalization was more commonly observed in males, without the difference reaching statistical significance (p = 0.101). With regard to the leukocyte count at the time of FN-related hospital admission, no statistically significant difference was found in leukocyte or total neutrophil counts; however, the monocyte count was not considered at admission. Pegfilgrastim-treated patients

were observed to recover leukocyte counts faster than those treated with filgrastim, with the number of blood product transfusions being higher in filgrastim-treated patients. Most patients experienced fever and neutropenia with no evident clinical focus, followed by respiratory tract infections and gastroenteritis, among others. Three patients treated with filgrastim and two with pegfilgrastim were admitted to the intensive-care department due to sepsis and/or shock. Average days of hospital stay was significantly higher in the group of chemotherapy courses that received filgrastim: 5.4  $\pm$  1.5 vs. 5.4  $\pm$  1.6 days in those treated with pegfilgrastim, p = 0.017 (Table 2). When the cost of FN events was analyzed in Mexican pesos in both treatment groups, the chemotherapy courses with filgrastim-based prophylaxis were observed to be a mean of \$ 16,206.3 ± 4,531.1 pesos, whereas in those treated with pegfilgrastim it was \$ 8,723.8  $\pm$  3,644 pesos, with the difference being statistically significant (p < 0.001). Global cost included hospitalization days, medications, transfusions, laboratory and imaging studies, etc., as well as the costs of the G-CSF drugs (filgrastim cost: \$ 1,200 per vial; pegfilgrastim: \$ 22,000 per vial; government prices), and we observed that prophylaxis with pegfilgrastim reduced the total cost covered by the institution by up to 25% approximately in comparison with the use of filgrastim. with total global cost of \$ 1,018,323 vs. 1,278,186, respectively (Fig. 2). Both groups required support with blood products: 12 hospitalized patients (46.1%) were transfused red blood cell concentrates and 11 patients (42%) platelet concentrates, with the difference being that those patients treated with filgrastim had grade 3 or 4 hematologic toxicity (Hb 6.5-8 g/dl and platelets 25-50,000/mm<sup>3</sup> for grade 3 or < 25,000/mm<sup>3</sup> for grade 4), thus requiring a higher number of red blood cell and platelet concentrates in comparison with those in whom pegfilgrastim was administered. However, it should be noted that this study only included blood product administration costs, without considering the cost related to obtain them (laboratory tests, double serology for each donor, equipment to obtain blood samples, use of laboratory equipment for each one of the blood products, etc.).

	Filgrastim (n = 53)	Pegfilgrastim (n = 53)	Р
Febrile neutropenia events*	26	9	0.000
Leukocyte count**	851 (100-1,150)/mm <sup>3</sup>	1,066 (160-1,240)/mm <sup>3</sup>	0.55
Absolute neutrophils <sup>†</sup>	204 (0-570)/mm <sup>3</sup>	208 (0-660)/mm <sup>3</sup>	0.95
Type of infection:			
<ul> <li>– FN without focus</li> </ul>	9	2	
<ul> <li>Respiratory tract infection</li> </ul>	7	4	
<ul> <li>Gastroenteritis</li> </ul>	6	0	
– Other	8	2	
Hospitalization days:			
Average (range)	5.4 (3-9)	3.7 (2-6)	0.017
Cost per neutropenia event⁺	\$ 16,206.00 ± 4,531.00	\$ 8,723.00 ± 3,644.00	0.001
Prophylactic treatment global cost‡	\$ 1,278,186.00	\$ 1,018,323.00	0.001

Table 2. Febrile neutropenia prophylaxis results in children with solid tumors treated with filgrastim vs. pegfilgrastim

\*Required hospitalization; <sup>†</sup>At febrile neutropenia-related hospital admission; <sup>‡</sup>Mexican pesos. FN: febrile neutropenia.



**Figure 1.** Global cost per febrile neutropenia event in pediatric patients with solid tumors prophylactically treated with pegfilgrastim vs. filgrastim (Mexican pesos).

In addition, in both groups there were patients who required management in the pediatric intensive-care department, which increased the costs owing to the serious condition of the patient, the continuous use of monitors, infusion pump, laboratory and imaging studies, and even parenteral nutrition, among others, with the difference being made by hospital-stay days. Another factor that modified this cost difference is the use of broad spectrum antimicrobial, antifungal, and antiviral agents in the required cases, without taking into account the outpatient use of antimicrobials that did not require hospitalization.

# DISCUSSION

In this cost-benefit study of primary prophylaxis with filgrastim vs. pegfilgrastim in cancer patients treated with myeloablative chemotherapy, only patients with FN episodes warranting hospital admission were considered, without those requiring transfusions or antimicrobial use in the outpatient setting being included. A decrease of 50-60% in FN events with the prophylactic use of G-CSF is reported in the international literature<sup>1,14</sup>. During the studied period, hospitalization was required in 33% of all courses. In the study by Eldar-Lissai, et al. the use of pegfilgrastim was reported to decrease FN-related hospitalizations by more than 90%; however, in our study, the difference in hospitalizations was 47 vs. 17% with the use of filgrastim and pegfilgrastim, respectively<sup>1</sup>. However, the overall cost of care was reduced with pegfilgrastim prophylactic administration, owing to savings associated with the decrease in FN events and in the FN degree of severity, with the reduction in the number of bed-days, including admission to the emergency department, management in different hospital departments such as infectology, intermediate therapy, or pediatric intensive therapy, laboratory and imaging studies, as well as the use of broad spectrum antimicrobials and transfusions and their efficacy, with efficacy being regarded as hematological recovery, taking into account both neutrophil and monocyte



Figure 2. Global cost of febrile neutropenia prophylaxis with filgrastim and pegfilgrastim in pediatric patients with solid tumors (Mexican pesos).

recovery<sup>20</sup>. Pegfilgrastim added cost is approximately \$22,000 per vial in comparison with the filgrastim cost of \$1,200; however, the latter is used for 10 days, which leads to a total cost of \$18,000 per chemotherapy course, with a 25% saving. However, this saving is not reflected in the number of FN events and their severity or in hospitalization costs. Another important benefit found with the use of pegfilgrastim is that, owing to the decrease in FN events and faster recovery, patients do not delay the next chemotherapy course, which may be reflected on survival, as has been reported in the international literature<sup>1,3,10,16,19</sup>.

Currently, there are few pharmacoeconomic studies available, and they are highly important, since they should serve as a tool for decision making. According to some studies, the use of the pegylated form has been found to be more efficacious than filgrastim, owing to a decrease in both costs and FN events<sup>1-16</sup>. The cost-efficacy analysis looking at life-years gained in survivor pediatric patients treated with filgrastim vs. pegfilgrastim is the subject of a new trial that has not yet concluded; however, it could be inferred that long-term efficacy will be demonstrated.

# CONCLUSIONS

Febrile neutropenia prophylaxis with pegfilgrastim has equal clinical and economic benefits as in adult patients; however, quality-adjusted life-years gained could be much higher in pediatric patients. The performance of pharmacoeconomic studies in our country is of vital importance in order to select the best treatment for our patients, while providing greater benefits.

# DECLARATION OF INTEREST

There is no conflict of interests since the study was NOT financed by the pharmaceutical industry. The costs related to this study were entirely financed by our institution.

# REFERENCES

- Eldar-Lissai A, Cosler LE, Culakova E, Lyman GH. Economic analysis of prophylactic pegfilgrastim in adult cancer patients receiving chemotherapy. Value Health. 2008;11:272-9.
- Aapro M, Crawford J, Kamioner D. Prophylaxis of chemotherapy-induced febrile neutropenia with granulocyte colony-stimulating factors: where are we now? Support Care Cancer. 2010;18:529-41.
- Cooper KL, Madan J, Whyte S, Stevenson MD, Akehurst RL. Granulocyte colony-stimulating factors for febrile neutropenia prophylaxis following chemotherapy: systematic review and meta-analysis. BMC Cancer. 2011;11:404.
- Kuderer NM, Dale DC, Crawford J, Cosler LE, Lyman GH. Mortality, morbidity and cost associated with febril neutropenia in adult cancer patients. Cancer. 2006;106:2258-66.
- Talcott JA, Whalen A, Clark J, Rieker PP, Finberg R. Home antibiotic therapy for low-risk cancer patients with fever and neutropenia: a pilot study of 30 patients based on a validated prediction rule. J Clin Oncol. 1994;12:107-14.
- Weycker D, Malin J, Barron R, Edelsberg J, Kartashov A, Oster G. Comparative effectiveness of filgrastim, pegfilgrastim, and sargramostim as prophylaxis against hospitalization for neutropenic complications in patients with cancer receiving chemotherapy. Am J Clin Oncol. 2012;35:267-74.
- Caggiano V, Weiss RV, Richert TS, et al. Incidence, cost and mortality of neutropenia hospitalization associated whit chemotherapy. Cancer. 2008:103:1916-24.
- Renwick W, Pettengell R, Green M. Use of filgrastim and pegfilgrastim to support delivery of chemotherapy: twenty years of clinical experience. BioDrugs. 2009;23:175-86.
- Aapro MS, Cameron DA, Pettengell R, et al. EORTC guidelines for the use of granulocyte colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2006;42:2433-53.
- Smith TJ, Khatcherssian J, Lyman GH, et al. Update of recommendations for the use of with blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006;24:3187-205.
- Lyman G, Lalla A, Barron R, Dubois RW. Cost-effectiveness of pegfilgrastim versus 6-day filgrastim primary prophylaxis in patients with non-Hodgkin's lymphoma receiving CHOP-21 in United States. Curr Med Res Opin. 2009;25:401-11.
- Talcott JA, Whalen A, Clark J, Rieker PP, Finberg R. Home antibiotic therapy for low-risk cancer patients with fever and neutropenia: a pilot study of 30 patients based on a validated prediction rule. J Clin Oncol. 1994;12:107-14.
- Lui Z, Doan QV, Malin J, et al. The economic value of primary prophylaxis using pegfilgrastim compared with filgrastim in patients with breast cancer in the UK. Appl Health Econ Health Policy. 2010;7:193-205.
- Whyte S, Cooper KL, Stevenson MD, Madan J, Akehurst R. Cost-effectiveness of granulocyte colony-stimulating factor prophylaxis for febrile neutropenia in breast cancer in the United Kingdom. Value Health. 2011;14:465-74.
- 15. Sehouli J, Goertz A, Steinle T, et al. [Pegfilgrastim vs filgrastim in primary prophylaxis of febrile neutropenia in patients with breast cancer after chemotherapy: a cost-effectiveness analysis for Germany]. Dtsch Med Wochenschr. 2010;135:385-9.
- Ishiguro H, Kondo M, Hoshi SL, et al. Economic evaluation of intensive chemotherapy with prophylactic granulocyte colony-stimulating factor for patients with high-risk early breast cancer in Japan. Clin Ther. 2010;32:311-26.

- Aapro MS, Bohlius J, Cameron DA, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumors. Eur J Cancer. 2011;47:8-32.
- Weycker D, Malin J, Kim J, et al. Risk of hospitalization for neutropenic complications of chemotherapy in patients with primary solid tumors receiving pegfilgrastim or filgrastim prophylaxis: a retrospective cohort study. Clin Ther. 2009;31:1069-81.
- Crawford J, Dale DC, Kuderer NM, et al. Risk and timing of neutropenic events in adult cancer patients receiving chemotherapy: the results of a prospective nationwide study of oncology practice. J Natl Compr Canc Netw. 2008;6:109-18.
- Scholz M, Ackermann M, Emmrich F, Loeffler M, Kamprad M. Effectiveness of cytopenia prophylaxis for different filgrastim and pegfilgrastim schedules in a chemotherapy mouse model. Biologics. 2009;3: 27-37.
- Johnston E, Crawford J, Blackwell S, et al. Randomized, dose-escalation study of SD/01 compared with daily filgrastim in patients receiving chemotherapy. J Clin Oncol. 2000;18:2522-8.
- Lyman GH, Kuderer N, Greene J, Balducci L. The economics of febrile neutropenia: implications for the use of colony-stimulating factors. Eur J Cancer. 1998;34:1857-64.
- Hirsch BR, Lyman GH. Pharmacoeconomics of the myeloid growth factors: a critical and systematic review. Pharmacoeconomics. 2012; 30:497-511.
- Colester LE, Sivasubramaniam V, Agboola O, et al. Effect of outpatient treatmen of febrile neutropenia on the risk threshold for the use of CSF in patients with cancer treated with chemotherapy. Value Health. 2005;8:47-52.
- Hershman DL, Wilde ET, Wright JD, et al. Uptake and economic impact of first-cycle colony-stimulating factor use during adjuvant treatment of breast cancer. J Clin Oncol. 2012;30:806-12.
- 26. Timmer-Bonte JN, Andag EM, Smit HJ, et al. Cost-effectiveness of adding granulocyte colony-stimulating factor to primary prophylaxis with antibiotics in small-cell lung cancer. J Clin Oncol. 2006;24: 2991-7.
- Costa LJ, Kramer C, Hogan KR, et al. Pegfilgrastim vs filgrastim based autologous hematopoietic stem cell mobilization in the setting of preemptive use of plerixafor: efficacy and cost analysis. Transfusion. 2012;52:2375-81.
- Sebban C, Lefranc A, Perrier L, et al. A randomised phase II study of the efficacy, safety and cost-effectiveness of pegfilgrastim and filgrastim after autologous stem cell transplant for lymphoma and myeloma (PALM study). Eur J Cancer. 2012;48:713-20.
- 29. Wannesson L, Luthi F, Zucca E, et al. Pegfilgrastim to accelerate neutrophil engraftment following peripheral blood stem cell transplant and reduce the duration of neutropenia, hospitalization, and use of intravenous antibiotics: a phase II study in multiple myeloma and lymphoma and comparison with filgrastim-treated matched controls. Leuk Lymphoma. 2011;52:436-43.
- 30. Aapro M, Cornes P, Abraham I. Comparative cost-efficiency across the European G5 countries of various regimens of filgrastim, biosimilar filgrastim, and pegfilgrastim to reduce the incidence of chemotherapy-induced febrile neutropenia. J Oncol Pharm Pract. 2012;18:171-9.
- Crokaert F. Febrile neutropenia in children. Klinische Padiatrie. 2008; (Suppl 1):S9-16.
- 32. Fox E, Widemann B, Hawkins DS, et al. Randomized trial and pharmacokinetic study of pegfilgrastim vs. filgrastim after dose-intensive chemotherapy in young adults and children with sarcomas. Clin Cancer Res. 2009;15:7361-7.


SOCIEDAD MEXICANA DE ONCOLOGÍA, A.C. GACETA MEXICANA DE ONCOLOGÍA WWW.gamo-smeo.com



#### ORIGINAL ARTICLE

### Clinical Genetics: Basic Concepts for Oncology Practice

# Clara Ibet Juárez-Vázquez<sup>1,\*</sup>, Ricardo Alejandro Lara-Aguilar<sup>1</sup>, Francisco Javier Ochoa-Carrillo<sup>2</sup> and Herbert García-Castillo<sup>1</sup>

<sup>1</sup>Life in Genomics, <sup>2</sup>Instituto Nacional de Cancerología and Hospital Ángeles del Pedregal; Mexico City, Mexico

Received for publication: 10 December 2016; accepted for publication: 25 February 2017 Available online: 10 July 2017

#### **KEYWORDS**

Genetics concepts; Genetics terms; Genetic counseling; Hereditary cancer **Abstract** Hereditary cancers are common in clinical oncology 5-10% of all diagnosed neoplasms are estimed to be hereditary cancer. Therefore, careful study of the family history, as well as knowledge of the basic principles of genetics is required to address this type of patient. The purpose of this article is to offer basic genetics concepts as a useful tool in oncology clinical practice with practical examples, as well as to justify why a genetics specialist should be part of the multidisciplinary team in patients with a suspected hereditary oncologic condition. (creativecommons.org/licenses/by-nc-nd/4.0/).

\*E-mail for correspondence: clarajuarez@lifeingenomics.com (C.I. Juárez-Vázquez)

http://dx.doi.org/10.24875/j.gamo.17000006

1665-9201 / © 2017 Sociedad Mexicana de Oncología. Publicado por Permanyer México. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

#### INTRODUCTION: PRINCIPLES OF INHERITANCE

Each trait that Mendel identified in pea plants, such as shape, color, size, etc., corresponds to the expression of a different gene. The phenotype refers to characteristics we observe (morphological, physiological or biochemical), such as the eye color, whereas the genotype is the genetic constitution. The expression and interaction of the genotype with the environment enable the phenotype. As an example, we can mention eye color, which corresponds to the phenotype, whereas the genotype refers to the variants of each gene that influences the determination of this trait.

The term "gene" is defined as a specific DNA fragment or sequence that determines a trait<sup>1,2</sup>; the gene is the fundamental unit of inheritance<sup>3</sup>, and each gene's different versions are known as "alleles" (alternative forms of a gene). For example, the *EYCL3* gene is one of the genes that determine the eye color in humans<sup>4</sup>, and there are two alleles for this gene: one for the blue (no brown) and one for the brown eye color.

All genes have a specific position within a chromosome, with this location being known as "locus"<sup>1</sup>; the *EYCL3* gene is at 15q11.2, which would translate as chromosome 15, long arm (q), band 11.2. This locus can be located by the allele for brown or blue (no brown) eye color<sup>4</sup>.

The basic structure of a gene is made up by variable sized DNA regions that encode for specific amino acids in the protein called "exons", while those regions in genes that do not encode for any amino acid are known as "introns" (Fig. 1)<sup>5</sup>.

#### HOMOZYGOTE AND HETEROZYGOTE: EQUAL AND DIFFERENT ALLELES

When both alleles in a locus are equal they are "homozygotes", and when they are different from each other they are known as "heterozygotes". In the eye color example, the brown color allele (B) dominates over the blue (no brown) color (b); this way, when a pair of different alleles (Bb) are present (heterozygocity), only the physical trait encoded by the dominant allele will be observed, i.e. brown eyes; conversely, blue-eyed (no brown-eyed) people would be homozygous for allele b (bb).

It should be noted that the above occurs as long as there is a specific combination of *EYCL3* and other genes' alleles, since eye color is a polygenic trait that is influenced by several genes that interact with the *EYCL3* gene.

#### EXAMPLE APPLIED TO ONCOLOGY

#### Cytochrome CYP2D6

Cytochrome P450 is a family of enzymes in charge of metabolizing certain drugs. Among them, the enzyme product of the *CYP2D6* gene metabolizes most parts of tamoxifen to convert it into its active metabolite, endoxifen. Most people normally metabolize tamoxifen; however, those who are homozygous for allele 4 (*CYP2D6\*4*/*CYP2D6\*4*) display the slow metabolizing phenotype and, therefore, tamoxifen metabolizes too slowly into endoxifen, which causes the treatment to be inefficacious. These patients are candidates to aromatase inhibitors such as letrozole rather than to tamoxifen. Heterozygotes with the *CYP2D6\*1/CYP2D6\*4* genotype are expected to exhibit the intermediate metabolizer phenotype and to have reduced endoxifen levels, which implies clinical inefficacy. In the Mexican population, a frequency of 3.1% of CYP2D6\*4 slow metabolizers has been found, as well as 20.7% of intermediate metabolizers, heterozygous for *CYP2D6\*4* (*i.e. CYP2D6\*1/CYP2D6\*4*)<sup>6</sup>.

The P450 cytochrome is an example of a gene that follows a Mendelian pattern of inheritance, where both alleles are expressed in the heterozygous status; i.e. it is a gene with a co-dominant pattern of inheritance. There are ongoing studies with large numbers of patients in order to determine if this pharmacogenetic study should be applied to all patients in routine clinical practice<sup>7</sup>.

#### **TYPES OF INHERITANCE**

In the human species, chromosomes are classified as sexual chromosomes (X, Y) and autosomes (pair 1 to 22), which are identical between both genders; for this reason, an autosomal disease implies that the gene that causes the disease will be present in the autosomes, and both genders are usually clinically affected. In X-linked conditions, such as hemophilia, the gene that causes the disease is in sexual chromosome X and it affects predominantly males<sup>1</sup>.

Diseases caused by a single gene in a specific locus are known as monogenic and follow a Mendelian inheritance pattern. An "autosomal dominant" disease occurs when a mutated allele produces the phenotype in spite of the other normal allele. On the other hand, "autosomal recessive" inheritance is observed when both chromosomes display the mutated allele; only homozygous individuals have the disease<sup>3</sup>.

#### PENETRANCE AND EXPRESSIVITY

Penetrance is defined as the percentage of individuals with a particular genotype that expresses the expected phenotype. When a genotype fails to produce the expected phenotype, this is known as "incomplete penetrance"<sup>1</sup>. Another related concept is "expressivity", which is defined as the level of expression of a trait determined by a gene. "Variable expressivity" represents the expression spectrum of a specific genotype. Both incomplete penetrance and variable expressivity result from gene interaction effects and environmental effects, which can alter or partially or totally suppress the effect of a particular gene and, therefore, the sole presence of an altered gene does not warrant its expression. The phenotype is the result of a genotype that is expressed in a specific environment, i.e. each genotype can produce several phenotypes according to environmental conditions and interactions with other genes where the development occurs<sup>1</sup>.

#### Example applied to oncology

The *BRCA* gene is a tumor-suppressor gene and is responsible for 60% of hereditary breast and ovarian cancer cases.

This gene takes care of DNA double-strand rupture repair, and is inherited in an autosomal dominant form, i.e. there is 50% risk that the offspring will inherit the mutant gene from affected parents. However, even if there is one affected allele, it will require the other allele to become damaged throughout life for cancer to be produced, which is known as the Knudson or two-hit theory (which will be explained later).

Penetrance of this gene is high but incomplete. Between 41 and 90% of people who inherit a mutation develop cancer sometime in their lifetime<sup>8</sup>. Expressivity is variable: some people develop breast cancer, others ovarian cancer and, in a lesser proportion, cancer in other organs such as the pancreas and the peritoneum. In males, prostate cancer is more common, although they can also develop breast cancer. It should be noted that there will also be patients who will develop more than one malignancy throughout their lives, and there is risk for contralateral cancer (64%) and ovarian cancer (44%) after a first breast cancer.

The risk of cancer in *BRCA*-mutation carriers increases with age owing to incomplete penetrance and variable ex-

**TILL 4 A 1 5 1 7 1 5 17 18** 

pressivity, but the development and onset of cancer cannot be accurately predicted<sup>3</sup>.

#### MUTATIONS AND POLYMORPHISMS

Changes in genetic information that are not explained by preexisting genetic variability recombination are known as "mutations". Mutations can be alterations in the number or structure of chromosomes or the result of changes in the DNA sequence, e.g. point mutations (changes or substitutions of one base for another)<sup>2</sup>.

Mutations are the source of evolution as they provide the raw materials for it to be carried out. Without mutations, genes would only exist in a single form and organisms would not be able to evolve and adapt to environmental changes<sup>2</sup>.

Polymorphisms are genetic variants present in more than 1% of the population, while mutations are present in less than 1%. Variants of a single nucleotide are known as single nucleotide polymorphisms (SNP), and are distinguished from point mutations by their frequency in the population<sup>3</sup>.

Table 1. Main types of initiations and a				
Type of mutation	Definition			
Substitution of one base	Changes the nitrogenous base of a single nucleotide of the original DNA for another different one.			
	Example: g.45576A>C, changes an adenine for a cytosine at genomic position 45576 of the gene.			
Insertion	One or more nucleotides added in the original DNA sequence.			
	Example: g.5756_5757insAGG, an insertion of the AGG nucleotides between positions 5756 and 5757, generating an increase of three bases in the gene sequence.			
Deletion	Elimination of one or more nucleotides in the DNA sequence.			
	Example: g.120_123del, a loss of nucleotides 120 to 123 of the gene sequence.			
Frameshift	Insertion or deletion of a number of nucleotides in the DNA (which is not divisible by three) that affects the original traduction of the protein.			
	Example: c.288_289dupCC (p.Arg97Profs*23) nucleotide 288 and 289 are duplicated (CC) resulting in a change of amino acid arginine 97, which is the first amino acid that changes for proline creating a new reading frame ending at stop codon in position 23.			
Expansion by trinucleotide repetition	Repeated sequence of three nucleotides that progressively increases in quantity, potentially altering the size of a gene.			
	Example: c.53GCA[80], an increase in the number of repeated GCA (the 3 nucleotides repeated 80 times) in the encoding sequence of the gene.			
Chromosomal	Alters the number or structure of one or more chromosomes, thus affecting many genes that generate important phenotypical changes.			
	Example: 47,XY, +21, trisomy 21, presence of an extra chromosome 21.			
Genomic	Alters the haploid number of the species causing polyploidy.			
	Example: 69,XXX, triploidy, presence of 3n, additional haploid complement.			
Missense	Changes the wild type amino acid codon for another different one, thus altering the function of the protein.			
	Example: c.4576A>C; p.Leu126Arg, the change of adenine for cytosine causes that wild type amino acid.			
Nonsense	Changes the wild type amino acid codon for a stop codon, which causes premature termination of the protein, leaving it without function.			
	Example: c.4576A>X; p.Leu126*, the change of adenine for another nucleotide causes the amino acid leucine to change for a protein termination codon.			
Silent	Change an encoding codon for another synonym; therefore, the amino acid sequence of the protein is not altered.			
	Example: c.4576A>C; p.Leu126=, in spite of the change of adenine for cytosine in the gene sequence, the new codon encodes for the same leucine amino acid.			

G: genomic sequence; p: protein sequence; c: coding DNA sequence.



Figure 1. Structure and localization of a gene.

Mutations can originate in any cell and at any stage of the cell cycle. If the mutation is produced in "somatic cells" (any cell but gametes), these cells produce identical daughter cells, which results in the mutation only being detectable in cells descending from the original cell where the mutation was initiated<sup>2</sup>. If a mutation occurs in "germ cells" (in any of the gametes: ovule[s] or spermatozoid[s]), its effects are likely to be immediately expressed in the offspring<sup>2</sup>; this mutation is present in all cells of an individual's body<sup>3</sup>. Table 1 illustrates the different types of mutations, as well as examples of nomenclature for each case.

#### CANCER GENES

A group of genes are the main regulators of cell cycle and cell division and death processes. Mutations in these genes are mainly responsible for the development of cancer<sup>3</sup>.

In general, mutations occurring in genes that promote cell growth and division are dominant, since it only takes a single cell of the gene to be mutated for its effect to be produced; these genes are known as "oncogenes". In healthy cells, oncogenes' non-mutated versions are known as "proto-oncogenes", which, when mutated, turn into oncogenes and contribute to the development of cancer<sup>1</sup>.

Some genes repress cell growth and division when inactivated by recessive mutations, stimulate cell division. This effect requires both gene copies to be mutated in order to block cell division inhibition; these genes are known as "tumor-suppressor genes". In this way, an organism can inherit a defective copy of the gene (heterozygous status) and not develop the disease since the other allele is wild-type (normal). However, heterozygous individuals are predisposed to develop cancer because wild-type allele inactivation is the only factor required to eliminate tumor-suppressor activity, a phenomenon known as "loss of heterozygocity" (LOH)<sup>1</sup>.

There is another group of genes called "DNA repair genes", usually tumor suppressor genes, which correct errors during cell division. Mutations in these genes making cells prone to accumulate mutational errors associated with several types of cancer (colorectal, endometrial and gastric cancer)<sup>1</sup>.

#### Examples applied to oncology

An example of an oncogene is the *KRAS* gene; having a proto-oncogene like this one mutated confers poor prognosis for tumors. It has been studied in colon cancer and lung cancer, among others; if it is mutated, chemotherapy with cetuximab or panitumumab is particularly not recommended owing to the low response rate.

With regard to tumor-suppressor genes, there are the mismatch DNA-repair genes and *MLH1*, responsible for 90% of Lynch syndrome or hereditary non-polyposis colorectal cancer, an autosomal-dominant syndrome of variable expressivity and incomplete penetrance. Although the most common cancer is in the colon, there is also risk for cancer in other organs such as the stomach, small intestine, pancreas, kidney, endometrium, and ovary. It occurs at 50 years of age on average in the form of adenocarcinomas, predominantly in the proximal colon. Patients with this mutation have 52-82% of risk of developing cancer throughout their lives<sup>9</sup>. The *MSH2* and *MLH1* genes correct mismatch errors during DNA replication; when mutated, they promote other genes' alteration<sup>3</sup>.

#### **CANCER IS A GENETIC DISEASE**

Normal cells carry out several processes in response to internal and external (stimulating or inhibitory) signals: they grow, divide, maturate, and die. In a cancer cell, some of these signals are interrupted, which makes the cell proliferate at an abnormally higher velocity owing to the loss of response to normal control mechanisms, in this way modifying the original shape and ultimately producing an abnormal cell mass.

Cancer arises due to DNA mutations that alter genes associated with cell-division regulation. Ionizing radiation and chemical substances are carcinogenic due to sometimes they break DNA at one or two of its strands, activating an oncogene. Viruses such as human papilloma virus produce cancer because they carry oncogenes that are able to confer immortality to the cells they infect. Other cancers are associated with chromosomal defects; in chronic myeloid leukemia there is a reciprocal translocation between chromosomes 9 and 22 that generates a hybrid *BCR-ABL* gene with oncogenic activity. Other cancers are of the hereditary type, owing to the inheritance of mutated tumor-suppressor genes<sup>1</sup>.

Most tumors have dozens of point mutations in several genes, and some cancers may have more than 200 mutations, with 95% of them being point mutations. However, many of these mutations are deemed to be "passenger mutations" and do not confer a selective growth advantage, whereas a few are "driver mutations", i.e. they promote tumorigenesis. A typical tumor has 2-8 driver mutations that are related to signaling pathways that regulate cell destiny, survival, and genomic maintenance processes<sup>10</sup>.

#### Example applied to oncology

Retinoblastoma is an autosomal-dominant disease caused by an alteration in tumor-suppressor gene *RB1*. Knudson's Hypothesis or double-hit theory explains the genetic basis of this cancer. Knudson proposed that retinoblastoma is caused by two different genetic defects and both have to occur for cancer to develop. In cases where the retinoblastoma is unilateral, a single cell suffers two successive mutations. In cases of bilateral retinoblastoma both eyes are prone to cancer development, Knudson proposed that the patient inherits one of the two mutations (one hit) in all cells of the both eyes, second mutation in one eye-cell (two hits) is required to cancer development. In cases of unilateral retinoblastoma a single cell suffers two successive mutations (two hits). It should be noted that in these hereditary cases there is also risk for other type of cancers such as sarcoma, osteosarcoma, and melanoma<sup>1</sup>.

### CLASSIFICATION OF CANCER BASED ON ITS GENETIC ORIGIN

#### Sporadic cancer

Sporadic cancer results from acquired, sequential, and non-corrected accumulation of mutations in somatic cells. Activation of mutations in oncogenes and inactivation of tumor-suppressor genes are probably sporadic tumor's first events, in addition to other independent mutations in at least 4-5 genes<sup>11</sup>. Another characteristic is the age of presentation is as expected for the type of cancer, generally it does not affect relatives, and usually there are aggregated environmental risk factors<sup>12</sup>.

#### Familial cancer

Familial cancer occurs in several members of one family. However, it is not possible to recognize inheritance patterns, usually there are no mutations in hereditary cancer genes, and an increased risk for the development of cancer is known to exist for relatives<sup>13</sup>.

#### Hereditary cancer

Hereditary cancer affects several members of a family and it is possible for inheritance patterns to be found. Generally, it occurs in people younger than expected for the type of cancer; these are more aggressive cancers and can be suspected based on clinical features. In hereditary cancers, it is important for germ mutations in one of the alleles of genes with high susceptibility for cancer to be identified. It is important to identify germline mutations in genes with high penetrance. For example, *BRCA1*, *BRCA2*, *PALB2*, *CHEK2*, *TP53* and *PTEN* in hereditary breast and ovarian cancer<sup>11,14</sup>.

#### GENETIC COUNSELING IN ONCOLOGY

Genetic counseling consists in offering information and guidance to the index case and his/her family about the role of genes and the possibility of their offspring inheriting the cancer risk, to explain international recommendations on currently available follow-up and even therapeutic and surgical strategies, as well as medical uncertainties and the available support to solve psychosocial problems. Finally, the benefits and limitations of molecular testing should be explained<sup>15</sup>. The risks for predisposition to cancer can vary among families due to the intervention of other modifier genes or the lifestyle<sup>15,16</sup>.

Genetic counseling is an essential part of cancer diagnosis and diagnosis and should be carried out by a medical geneticist in Mexico. Adequate genetic counseling should be carried out before and after a molecular test is indicated<sup>15</sup>.

#### CONCLUSIONS

Basic clinical genetics concepts were introduced, including topics about mutations, polymorphisms, nomenclature notions, types of inheritance, as well as some interesting applications in the fields of pharmacogenetics, oncogenesis, hereditary cancers, and genetic counseling, which in future issues will be addressed in depth. Knowledge of the principles of genetics applied to clinical oncology will enable a comprehensive management of the patient and better understanding of genetic studies in the oncology practice.

#### ACKNOWLEDGEMENTS

We thank Dr. Silvia Vidal Millán for her valuable comments in the preparation of the present manuscript.

#### REFERENCES

- Pierce BA. Fundamentos de genética. Conceptos y relaciones. Editorial Médica Panamericana; 2011.
- 2. Gardner EJ. Principios de Genética. Editorial LimusaWiley; 1998.
- Nussbaum RL. Thompson & Thompson, Genetics in Medicine. Editorial Saunders; 2004.
- Eiberg H, Mohr J. Assignment of genes coding for brown eye colour (BEY2) and brown hair colour (HCL3) on chromosome 15q. Eur J Hum Genet. 1996;4:237-41.
- Salazar-Montes A. Biología Molecular. Fundamentos y aplicaciones en las ciencias de la salud. Editorial Mc Graw Hill; 2013.
- Contreras AV, Monge-Cazares T, Alfaro-Ruiz L, et al. Resequencing, haplotype construction and identification of novel variants of CYP2D6 in Mexican Mestizos. Pharmacogenomics. 2011;12:745-56.
- Hoskins JM, Carey LA, McLeod HL. CYP2D6 and tamoxifen: DNA matters in breast cancer. Nat Rev Cancer. 2009;9:576-86.
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian, 2017. Available at: https://www.nccn.org/professionals/ physician\_gls/f\_guidelines.asp (Accessed Jan 15, 2017).
- National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, 2017. Available at: https://www.nccn.org/professionals/ physician\_gls/f\_guidelines.asp (Accessed Jan 15, 2017).
- Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz LA Jr, Kinzler KW. Cancer genome landscapes. Science. 2013;339:1546-58.
- 11. Kenemans P, Verstraeten RA, Verheijen RHM. Oncogenic pathways in hereditary and sporadic breast cancer. Maturitas. 2004;49:34-43.
- Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med. 2001;344:276-85.
- American Cancer Society. Genes and Cancer. Available at: http:// www.cancer.org/acs/groups/cid/documents/webcontent/002550-pdf.pdf (Accessed December 31, 2016).
- 14. ACOG Committee opinion no. 634: Hereditary cancer syndromes and risk assessment. Obstet Gynecol. 2015;125:1538-43.
- Vidal Millán S. Cáncer de Mama Hereditario: Identificación y Elección de Pacientes para Estudio Molecular de los Genes BRCA. Cancerología. 2008;3:51-61.
- Ochoa-Carrillo FJ, Millán SV. [Importance of genetic counseling and molecular diagnosis testing in families at high risk for cancer]. Cir Cir. 2006;74:137-42.



#### **REVIEW ARTICLE**

### Radiotracers Used in Nuclear Medicine for Prostate Cancer Diagnosis and Follow-Up

sociedad mexicana de oncología, a.c. GACETA MEXICANA

DE ONCOLOGI

www.gamo-smeo.com

#### Francisco O. García-Pérez and Sevastián S. Medina Ornelas\*

Department of Nuclear Medicine and Molecular Imaging, Instituto Nacional de Cancerología, Mexico City, Mexico

Received for publication: 16 December 2016; accepted for publication: 25 February 2017 Available online: 10 July 2017

KEYWORDS Radiotracer; Prostate cancer; Nuclear medicine;

PET/CT

**Abstract** Prostate cancer is the most common cause of cancer in males worldwide. Currently, imaging in prostate cancer has acquired great importance in staging, re-staging, treatment selection, and recurrence assessment. Molecular imaging with positron-emission tomography has enabled a personalized approach for these purposes. In addition to these clinical needs, there are growing perspectives and a challenge for new molecular imaging techniques, not only to detect metastatic disease, but also to provide relevant information on tumor biology and prognosis, and one of the greatest challenges for non-radioisotope imaging techniques is the ability to detect recurrence in patients with low levels of prostate-specific antigen. (creativecommons.org/licenses/by-nc-nd/4.0/).

PERMANYER

\*E-mail for correspondence: dr.sevastian@outlook.com (S.S. Medina Ornelas)

http://dx.doi.org/10.24875/j.gamo.17000007

1665-9201 / © 2017 Sociedad Mexicana de Oncología. Publicado por Permanyer México. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

#### INTRODUCTION

According to GLOBOCAN 2012 data, 14,016 patients are diagnosed with prostate cancer (PC) every year in Mexico, which represents 9.5% of all newly diagnosed tumors in the country, with this malignancy occupying the first place among males and females. In males, it is at first place, with 21.4% of all newly diagnosed tumors<sup>1,2</sup>.

Imaging plays an important role in PC, including accurate evaluation of disease extension, assessment of the site of recurrence, and monitoring of treatment response. Nuclear medicine imaging techniques are among the most novel results of investigations associated with image acquisition in PC, which enables better assessment than a few years ago<sup>3-5</sup>.

Several radiotracers for scintigraphy plus single-photon emission computed tomography (SPECT) and positron-emission tomography (PET) are currently commercially available in our country and many others are under investigation.

The purpose of the present review is to offer a current summarized perspective on the different radiotracer options used in nuclear medicine, both for scintigraphy and PET/CT, but especially on the usefulness of each one of them according to the patient's clinical scenario.

### RADIOTRACERS USED FOR SCINTIGRAPHY PLUS SPECT/CT

#### 99mTc-MDP

Bone scintigraphy with 99mTc-radiolabelled bisphosphonates is perhaps one of the most widely performed studies in nuclear medicine with the purpose to detect bone metastases. Osteoblasts form the osteoid matrix that subsequently will be mineralized by hydroxyapatite crystals. 99mTc-MDP (methylene diphosphonate) binds to hydroxyapatite crystals by chemo-adsorption proportionally to two situations: blood flow and osteoblastic activity<sup>6,7</sup>.

According to the National Comprehensive Cancer Network (NCCN), bone scintigraphy is indicated in patients with prostate-specific antigen (PSA) levels > 20 ng/ml, Gleason  $\geq$  8, T3, T4, or T2 if PSA > 10 ng/ml, or if there are symptoms present<sup>8</sup>. It is a highly sensitive method to detect bone metastases, especially osteoblastic. It can also be used to assess treatment response, although not semi-quantitatively as in the case of PET/CT<sup>9</sup>.

One of the greatest advantages of bone scintigraphy is that it requires a minimum of 5% bone turnover rate to be able to detect a lesion, whereas with anatomic studies such as X-ray, a minimum of 40-50% turnover is required for lesions to be visualized. This feature provides elevated sensitivity for the detection of bone metastases, which can be as high as  $96.9\%^{10}$ . However, the greatest disadvantage of this study is its low specificity, which can range from 41 to  $57\%^{10,11}$ . For this reason, hybrid equipment (SPECT/CT) allows for such specificity to be improved by merging the findings with a CT study, with up to 82% specificity being attained (Fig. 1)<sup>11</sup>.



Figure 1. Two-projection full body bone scintigraphy, where abnormal uptake focal increase is observed at the level of the right acetabulum and L4 (left). It is complemented with the SPECT/CT technique for better characterization (below).

#### 99mTc-PSMA

The prostate-specific membrane antigen (PSMA) is a full-membrane, type II glycoprotein that was identified as a homolog of type I folate hydrolase protein. In the central nervous system, it cleaves the NAAG (N-acetyl-1-aspartyl-1-glutamate) neurotransmitter into NAA (N-acetyl-aspartate) and glutamate. In malignant tissues, PSMA has been shown to be strongly expressed in the stroma adjacent to the neo-vasculature of multiple solid tumors<sup>12-15</sup>.

In PC, overexpression is associated with tumor grade, aneuploidy, and biochemical recurrence. An important characteristic of this radiotracer is that it is overexpressed when tumors become androgen-independent<sup>16</sup>.

The availability of gamma cameras and hybrid equipment at different hospital centers in comparison with PET/ CT equipment remains centralized; for this reason, labeling this novel agent with a more available radionuclide such as 99mTc has been attempted.

However, there are no reported studies in the literature reflecting the sensitivity and specificity since it is still under investigation, although the results so far are highly promising, even comparable to those with 68Ga-PSMA (Fig. 2).

#### 99mTc-Bombesin

Gastrin-releasing peptide receptors (GRPR) are G protein-coupled receptors that are overexpressed in many solid tumors, including PC. Bombesin is a 14-amino acid peptide that binds with high affinity to GRPR. Some studies have demonstrated that GRPR expression depends on the Gleason score in such a way that the higher the Gleason score, the lower the expression of these receptors will be<sup>17,18</sup>.

Only a few authors have reported on the safety and efficacy of radiolabeled bombesin analogs in PC, with a strong correlation being found with GRPR expression in patients with PC and in patients without the disease.

Figure 2. Full-body SPECT/CT with 99mTc-PSMA, where usual biodistribution and multiple metastasis-associated abnormal uptake zones are observed (left). Study carried out in the same patient with 68Ga-PSMA (right), where, at maximum intensity projection, the same bio-distribution and very similar abnormal uptake are observed, unlike a lesion at the level of the sternum visualized in the study with SPEC/CT, which is explained by the fact that this study was performed three weeks later.

Scopinaro, et al. demonstrated high affinity of the radiotracer in the primary tumor in 8/10 patients, and lymph node involvement in three patients<sup>19</sup>.

De Vincentis, et al. studied 14 patients with suspected PC, and found true-positives in 12 of them with confirmed histology, and true-negatives in the rest, with similar results to Scopinaro's findings in terms of lymph node involvement<sup>20</sup>.

Other studies show similar results as well as the same limitations in bone metastasis visualization since this agent has poor sensitivity for the detection of metastatic bone involvement, owing to the fact that the GRPR expression pattern in PC bone metastasis is different to that found in the primary tumor or lymph node involvement (Fig. 3).

Radiotracers using GRPR-antagonist agents have been recently found to be superior to those using agonists. Most recent investigations have focused on these agents for PET/CT, but marked with radionuclides such as 68Ga and  $64Cu^{21}$ .

#### RADIOTRACERS EMPLOYED FOR PET/CT

#### 18F-NaF

Sodium fluoride (NaF) is a radiotracer with similar properties to 99mTc-MDP, but minimal binding to proteins, rapid firststep extraction, and higher clearance from soft tissue, which allows twofold higher bone uptake, thus attaining a better target/background ratio. After chemo-adsorption onto the hydroxyapatite crystals, the 18F ion is rapidly exchanged for the hydroxyl ion (OH) on the hydroxyapatite matrix surface to form fluorapatite, with this incorporation being slow<sup>22,23</sup>.

The 18F-NaF uptake, the same as 99mTc-MDP, is conditioned by blood flow and bone remodeling, and uptake indicates osteoblastic activity by identifying reactive changes on the underlying involved bone area. However, abnormal uptake is not a phenomenon exclusive to metastases since any process with increased bone remodeling can display ab-



Figure 3. Full-body scintigraphy with 99mTc-Bombesin (left) in a patient with multiple bone metastases and prostate-specific antigen of 320 ng/ml; note that only some correspond to the blastic metastases observed in the bone scintigraphy (right).



Figure 4. Full-body bone scintigraphy anterior projection (left), where abnormal uptake focal increase is observed at the level of multiple vertebral bodies and minimal uptake in the pelvis. It is complemented with SPECT/CT technique (above), where blastic lesions at the level of the right ilium bone and at both sacrum bones with minimum radiopharmaceutical uptake are observed. Study carried out in the same patient with 18F-NaF (right), with macrophage inflammatory protein showing very similar abnormal uptake, with better target/background ratio, and which avidly concentrate the radiotracer in the merged image (below).

normal uptake, including trauma, arthritis, metabolic bone disease, osteomyelitis, surgical procedures at the bone level, and even visceral calcification<sup>24,25</sup>.

Several studies have compared the sensitivity and specificity of 99mTc-MDP with regard to 18F-NaF, with superiority of the latter being demonstrated for the detection of blastic-type metastatic bone disease (Fig. 4), with a sensitivity of 86.7-100% and specificity of 44-88.6%, and there are even some reports that show a specificity close to  $100\%^{10,26,27}$ .

Perhaps the greatest disadvantage of the study is the higher exposure to radiation, since total effective dose for PET/CT with 10 mCi (370 MBg) of 18F-NaF ranges from 8.9-12.1 mSv. in comparison with approximately 5.3-7.4 mSv for SPECT with 25 mCi (925 MBg) of 99mTc-MDP<sup>28</sup>.

#### 11C-Choline/18F-FCH

Choline (CH) can be labeled both with Fluor-18 (18F) and carbon-11 (11C). It enters into the cell by means of choline transporters and is the precursor for phospholipid biosynthesis, which is the main component of the cell membrane<sup>29</sup>.

Some tumors, particularly the prostatic tumor, show an increase in cell membrane synthesis as a consequence of uncontrolled cell proliferation, which is driven by choline kinase overexpression. This enzyme catalyzes choline phosphorylation to form phosphorylcholine, followed by the generation of phosphatidylcholine on tumor cell membrane. Choline uptake in PC appears to be affected by hypoxia, but it may not be correlated with cell proliferation<sup>30</sup>.

The usefulness of this agent is wide, and it ranges from detection to recurrence assessment<sup>31</sup>.

Different studies have demonstrated that PET/CT with 11C-choline has a sensitivity of 55-100% and specificity of 62-86% for the detection of the primary tumor. Partly, this broad range is due to important parameters such as tumor size, grade, and location, as well as PSA level, and even when sensitivity is elevated, it can be as low as 22% in case of extension beyond the prostate<sup>32,33</sup>.

With regard to the detection of recurrence after radical prostatectomy, international studies report a sensitivity of 64-78% and specificity of 88-90%34,35. Detection is strongly associated with PSA levels, since higher PSA levels, PSA high velocity, or lower PSA duplication time are related to higher rates of detection. The likelihood of detection increases with PSA levels > 2.4 ng/ml, PSA duplication time < 3.4 months, or when velocity is < 1 ng/ml/year when PSA levels are < 2.4 ng/ml. For this reason, the detection rate varies even in the localization of bone metastases<sup>36,37</sup> (Fig. 5).

One of the greatest disadvantages of 11C-choline is its short half-life, since this is only 20-minutes long, which makes it more expensive and difficult to distribute. In view of this, it can be labeled with 18F-FCH (18F-fluoromethylcholine), which has shown a very similar role in the detection of recurrence in comparison with 11C-choline. Pelosi, et al. reported a detection rate of 20% for 18F-FCH in patients with PSA levels < 1 ng/ml, 44% for levels of 1-5 ng/ml, and 82% for levels > 5 ng/ml, similar to findings reported by Krause, et al. for 11C-choline, with a detection rate of 36% for PSA levels < 1 ng/ml, 62% for levels of 2-3 ng/ml, and 73% for levels >  $3 \text{ ng/ml}^{38,39}$ .

#### 11C-Acetate

Acetate is a molecule that rapidly enters the cell by means of monocarboxylate transporters, where it is converted into acetyl-CoA by the action of acetyl-CoA synthetase, and this way it can be incorporated into two metabolic pathways, an anabolic and a catabolic one, with the pathway depending on the cell type.

Figure 5. Anterior macrophage inflammatory protein, where 11C-choline radiotracer normal distribution is observed, where, in addition, abnormal focal uptake is observed at the level of two lymph nodes of the left

In PC tumor cells, the fatty acid synthase enzyme is overexpressed, thus converting the most part of fatty acids acetate and being incorporated in phosphatidylcholine intracellular micro-domains (anabolic pathway), which are substrates for tumor growth. Fatty acid synthase overproduction is associated with higher tumor aggressiveness. The catabolic pathway influences as well, with acetate being able to metabolize into CO, via the Krebs cycle. Acetate is used as a substrate in some intracellular processes within the mitochondria by producing energy and in the cytosol in the synthesis of lipids<sup>40,41</sup>.

internal and external iliac chain, which is consistent with recurrence in a

prostate cancer patient with prostate-specific antigen levels of 5.9 ng/ml.

The 11C-acetate is unable to distinguish between benign prostatic hyperplasia (BPH) and prostate cancer. Data available to date report that sensitivity and specificity with regard to detection and evaluation of lymph node involvement are quite heterogeneous, since the results of studies with larger numbers of patients range from 73-88% for sensitivity and 29-41% for specificity in the detection of the primary tumor, whereas for lymph node staging, sensitivity ranges from 38-90% and specificity ranges from 67-96%, since the higher the PSA level is, the higher the specificity will be<sup>42,43</sup>.

The greatest usefulness of this agent is in disease localization in case of biochemical recurrence, where the detection rate will also be highly influenced by PSA levels: using a PSA duplication velocity > 1.32 ng/ml it will have 74% sensitivity and 75% specificity, whereas an accuracy of up to 59% will be obtained in patients with PSA levels > 3 ng/ml, and it will be as low as 4% if PSA levels are lower (Fig. 6)<sup>44,45</sup>.

#### **18F-FDG**

Cell membrane glucose transporter 1 (GLUT1) increased levels and hexokinase-mediated enzyme activity increase found in most tumors drive to intra-tumor increased metabolic activity. The GLUT1 expression is strongly upregulated in androgen-dependent and non-androgen-dependent prostate





Figure 6. Anterior macrophage inflammatory protein, where 11C-acetate radiotracer normal bio-distribution is observed, in addition to focal abnormal uptake at the level of a left external iliac chain adenopathy and axial and appendicular skeleton important diffuse uptake, with expansive lesions at the level of the right iliac bone, consistent with recurrence in a patient with castration-resistant prostate cancer with prostate-specific antigen levels of 58.1 ng/ml.



**Figure 7.** Anterior macrophage inflammatory protein, where 18F-FDG radiotracer normal bio-distribution is observed, in addition to abnormal uptake at the level of mediastinal lymph nodes and right internal and external lymph node chain, and at the bone level in a patient with prostate cancer progressing to six docetaxel cycles, with prostate-specific antigen levels of 58 ng/ml.

cells, with high levels of this transporter being found both in PC and BPH. In addition, 18F-FDG (fluorodeoxyglucose) normal urinary elimination route makes it a poorly sensitive or specific radiotracer in the detection of the primary tumor<sup>46</sup>.

Some studies have demonstrated its usefulness in this scenario: in one meta-analysis of 47,925 patients who underwent PET/CT, a PC prevalence of 1.8% was demonstrated for those with uptake incidental finding; however, with the advent of other radiotracers, its indication might be assigned to other conditions<sup>47</sup>.

In the setting of biochemical recurrence, there are some studies demonstrating its usefulness. Öztürk, et al. demonstrated a sensitivity of 61.6% and specificity of 75% after definitive treatment (radical prostatectomy or radiotherapy)<sup>48</sup>.

In a comparative trial of 18F-FDG with 11C-choline, the combination of both radiotracers was found to increase sensitivity by up to 80% and specificity by up to 40% in patients with PSA levels >  $1.9 \text{ ng/ml}^{49}$ .

Due to the heterogeneity in these types of tumors, treatment response can sometimes be seriously compromised. After treatment, the metabolism of lesions usually decreases; however, some lesions may have their metabolism decline and others not, and in some cases even not being correlated with the biochemical response. On the other hand, it can make the management be changed in up to 35% of patients according to the National Oncology PET Registry of the USA<sup>50</sup>.

The use of 18F-FDG can be useful in the detection of metastatic disease. A study conducted by Damle, et al. demonstrated 71.9% sensitivity and 100% specificity in the detection of bone metastases, which perhaps is currently the most widely accepted indication for the use of this tracer (Fig. 7), although with the use of new radiotracers it might not be the best option anymore<sup>10,43,46</sup>.

#### 68Ga-PSMA

As previously mentioned, the detection of early recurrence is one of the greatest challenges for imaging studies. The PSMA characteristics make it highly valuable by possessing the capability for early detection of progression or recurrence after androgen-deprivation therapy, even with low PSA levels (< 2 ng/ml)<sup>16,43</sup>.

In a study carried out by Afshar-Oromieh, et al., they found up to 84% of primary PC true-positives in a cohort of 37 patients, with 60% being found in patients with PSA levels < 2.2 ng/ml, whereas in those with PSA levels > 2.2 ng/ml, 100% were found<sup>51</sup>.

In another study, 18F-FCH was compared with 68Ga-PSMA for restaging in patients with PSA levels ranging from 0.01 to 116 ng/ml. Lesions were detected with 68Ga-PSMA in 87% of patients, whereas lesions were detected with 18F-FCH in only 70%, with PSA levels also having an influence<sup>52</sup>.

Eiber, et al., in a cohort of 245 patients with biochemical recurrence, demonstrated a detection rate of 96.8, 93.0, 72.7, and 57.9% in subjects with PSA levels > 2.1, < 2.0-1.0, < 1.0-0.5, and < 0.5-0.2 ng/ml, respectively (Fig. 8)<sup>53</sup>. In this way, this radiotracer has a higher detection rate compared with other radiotracers recommended in the literature, such as 11C-choline with a detection rate of 34-88%, 18F-choline with 43-79%, and 11C-acetate with a detection rate of 59-80%<sup>16,43</sup>.

#### 68Ga-DOTATOC/NOC

68Ga-DOTATOC is a radiotracer with affinity to somatostatin receptors (SSTR) 2 and 5, whereas 68Ga-DOTANOC displays affinity to SSTR 2, 3, and 5, which are commonly used in PET/CT studies to characterize neuroendocrine neoplasms<sup>54</sup>.





**Figure 8.** Anterior macrophage inflammatory protein, where 68Ga-PSMA radiotracer normal bio-distribution is observed, in addition to intense abnormal uptake being observed at the bone level, at the para-aortic lymph node level, and hepatic level, with the latter not being tomographically visualized, in a patient with prostate cancer progressing to six docetaxel cycles and three doses of 223Ra, with prostate-specific antigen levels of 78 ng/ml.



Figure 9. Anterior macrophage inflammatory protein, where 68Ga-DOTATOC radiotracer normal bio-distribution is observed, where also abnormal uptake at the bone level is observed, as well as at the deep left inguinal lymph node level, with the latter not being visualized with other radiotracers, in a patient with prostate cancer with neuroendocrine differentiation progressing to five docetaxel cycles and two doses of 223Ra, with prostate-specific antigen levels of 11 ng/ml.

The presence of SSTR in PC is related to a phenomenon known as "neuroendocrine differentiation", which indicates an adverse prognosis. In prostatic adenocarcinoma, an increased presence of non-androgen receptor-expressing neuroendocrine cells has been postulated to exist; therefore, they are androgen-independent so that they establish autocrine and paracrine networks to regulate growth and differentiation independently of the androgenic stimulus<sup>55</sup>.

There are not many currently existing reports demonstrating the usefulness of this radiotracer in this rather infrequent process in a large number of patients, and most publications have therefore been case reports demonstrating its usefulness, where it can be indicated in patients not responding to androgen-deprivation therapy with PSA elevation and where no disease is evidenced by other radiotracers (used in PET/CT) (Fig. 9)<sup>56,57</sup>.

#### CONCLUSION

There is substantial progress in the development and research of new radiotracers used by nuclear medicine for PC. A large volume of scientific literature has been produced over the past few years, demonstrating the potential usefulness of nuclear medicine in PC for a wide variety of indications. These advances have enabled better treatment selection for patients. Our better understanding on the early detection of local and distant recurrence is giving way to better assessment of patients with increased PSA levels after therapy, thus enabling the administration of novel therapies, including 223Ra, 177Lu-PSMA, and 225Ac. We hope these advances in molecular imaging may contribute to increase patient's quality of life and decrease PC-related mortality.

#### DECLARATION OF INTEREST

The authors declare not having any conflicts of interests.

#### ACKNOWLEDGEMENTS

The authors express their gratitude to the entire Nuclear Medicine Department of the Instituto Nacional de Cancerología.

#### REFERENCES

- Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available at: http://globocan.iarc.fr [Accessed September 20, 2016].
- Erazo-Valle A, Martinez-Cedillo J, Rivera-Rivera S, et al. Reunión de panel de expertos en cáncer de próstata. Gaceta Mex Oncología. 2014;13(Supl 2):2-17.
- Hricak H, Choyke PL, Eberhardt SC, Leibel SA, Scardino PT. Imaging prostate cancer: a multidisciplinary perspective. Radiology. 2007;243:28-53.
- Ibrahim N, Cho SY. Prostate cancer imaging: positron-emission tomography perspectives. Rep Med Imag. 2015;8:51-62.
- Bouchelouche K, Choyke P, Turkbey B. Advances in imaging modalities in prostate cancer. Curr Opin Oncol. 2015;27:224-31.

- 6. Dávila D, Antoniou A, Chaudhry MA. Evaluation of osseous metastasis in bone scintigraphy. Semin Nucl Med. 2015;45:3-15.
- 7. Brenner AI, Koshy J, Morey J, Lin C, DiPoce J. The bone scan. Semin Nucl Med. 2012;42:11-26.
- Prostate cancer. In National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, version 1.2016. National Comprehensive Cancer Network.
- Dennis ER, Jia X, Mezheritskiy IS, et al. Bone scan index: a quantitative treatment response biomarker for castration-resistant metastatic prostate cancer. J Clin Oncol. 2012;30:519-24.
- 10. Damle NA, Bal C, Bandopadhyaya GP, et al. The role of 18F-fluoride PET-CT in the detection of bone metastases in patients with breast, lung and prostate carcinoma: A comparison with FDG PET/CT and 99mTc-MDP bone scan. Jpn J Radiol. 2013;31:262-9.
- Helyar V, Mohan HK, Barwick T, et al. The added value of multislice SPECT/CT in patients with equivocal bony metastasis from carcinoma of the prostate. Eur J Nucl Med Mol Imaging. 2010;37:706-13.
- Mease RC, Foss CA, Pomper MG. PET imaging in prostate cancer: focus on prostate-specific membrane antigen. Curr Top Med Chem. 2013;13:951-62.
- Conway RE, Petrovic N, Li Z, Heston W, Wu D, Shapiro LH. Prostate-specific membrane antigen regulates angiogenesis by modulating integrin signal transduction. Mol Cel Biol. 2006;26:5310-24.
- Nomura N, Pastorino S, Jiang P, et al. Prostate specific membrane antigen (PSMA) expression in primary gliomas and breast cancer brain metastases. Cancer Cell Int. 2014;20:14-26.
- Chang SS, Reuter VE, Heston WD, Bander NH, Grauer LS, Gaudin PB. Five different anti-prostate-specific membrane antigen (PSMA) antibodies confirm PSMA expression in tumor-associated neovasculature. Cancer Res. 1999;59:3192-8.
- Lütje S, Heskamp S, Cornelissen AS, et al. PSMA ligands for radionuclide imaging and therapy of prostate cancer: Clinical status. Theranostics. 2015;5:1388-401.
- Markwalder R, Reubi JC. Gastrin-releasing peptide receptors in the human prostate: relation to neoplastic transformation. Cancer Res. 1999;59:1152-9.
- Sun B, Halmos G, Schally AV, Wang X, Martínez M. Presence of receptors for bombesin/gastrin-releasing peptide and mRNA for three receptor subtypes in human prostate cancers. Prostate. 2000;1;42:295.
- Scopinaro F, De Vincentis G, Varvarigou AD, et al. 99mTc-bombesin detects prostate cancer and invasion of pelvic lymph nodes. Eur J Nucl Med Mol Imaging. 2003;30:1378-82.
- De Vincentis G, Remediani S, Varvarigou AD, et al. Role of 99mTc-Bombesin scan in diagnosis and staging of prostate cancer. Can Biother Radiopharm. 2004;19:81-4.
- Mansi R, Minamimoto R, Mäcke H, lagaru AH. Bombesin-targeted PET of prostate cancer. J Nucl Med. 2016;57:67-725.
- Grant FD, Fahey FH, Packard AB, Davis RT, Alavi A, Treves ST. Skeletal PET with 18F-fluoride: applying new technology to an old tracer. J Nucl Med. 2008;49:68-78.
- Czernin J, Satyamurthy N, Schiepers C. Molecular mechanisms of bone 18F-NaF deposition. J Nucl Med. 2010;51:1826-9.
- Even-Sapir E, Mishani E, Flusser G, Metser U. 18F-fluoride positron emission tomography and positron emission tomography/computed tomography. Semin Nucl Med. 2007;37:462-9.
- 25. Fonager RF, Zacho HD, Langkilde NC, Petersen LJ. 18F-fluoride positron emission tomography/computed tomography and bone scintigraphy for diagnosis of bone metastases in newly diagnosed, high-risk prostate cancer patients: study protocol for a multicentre, diagnostic test accuracy study. BMC Cancer. 2016;16:10.
- Even-Sapir E, Metser U, Mishani E, Lievshitz G, Lerman H, Leibovitch

   The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP planar bone scintigraphy, single- and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT. J Nucl Med. 2006;47:287-97.
- Even-Sapir E, Metser U, Flusser G, et al. Assessment of malignant skeletal disease with 18F-fluoride PET/CT. J Nucl Med. 2004;45:272-8.
- Bastawrous S, Bhargava P, Behnia F, Djang DS, Haseley DR. Newer PET application with an old tracer: Role of 18F-NaF skeletal PET/CT in oncologic practice. Radiographics. 2014;34:1295-316.
- Janardhan S, Srivani P, Sastry GN. Choline kinase: an important target for cancer. Curr Med Chem. 2006;13:1169-86.
- Hara T, Bansal A, DeGrado TR. Effect of hypoxia on the uptake of [methyl-3H]choline, [1-14C]acetate and [18F]FDG in cultured prostate cancer cells. Nucl Med Biol. 2006;33:977-84.

- Schwarzenböck S, Souvatzoglou M, Krause BJ. Choline PET and PET/ CT in primary diagnosis and staging of prostate cancer. Theranostics. 2012;2:318-30.
- Scher B, Seitz M, Albinger W, et al. Value of 11C-choline PET and PET-CT in patients with suspected prostate cancer. Eur J Nucl Med Mol Imaging. 2007;34:45-53.
- 33. Giovacchini G, Picchio M, Coradesschi E, et al. 11C-choline uptake with PET/CT for the initial diagnosis of prostate cancer: relation to PSA levels, tumor stage and anti-androgenic therapy. Eur J Nucl Med Mol Imaging. 2008;35:1065-73.
- 34. Picchio M, Briganti A, Fanti S, et al. The role of choline positron emission tomography/computed tomography in the management of patients with prostate-specific antigen progression after radical treatment of prostate cancer. Eur Urol. 2011;59:51-60.
- Rinnab L, Mottaghy FM, Blumstein NM, et al. Evaluation of [11C]choline positron emission tomography in patients with increasing prostate-specific antigen levels after primary treatment for prostate cancer. BJU Int. 2007;100:786-93.
- Picchio M, Spinapolice EG, Fallanca F, et al. [11C]choline PET/CT detection of bone metastases in patients with PSA progression after primary treatment for prostate cancer: comparison with bone scintigraphy. Eur J Nucl Med Mol Imaging. 2012;39:13-26.
- Castellucci P, Fuccio C, Nanni C, et al. Influence of trigger PSA and PSA kinetics on 11C-choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy. J Nucl Med. 2009;50:1394-400.
- Pelosi E, Arena V, Skanjeti A, et al. Role of whole-body (18F)-choline PET/CT in disease detection in patients with biochemical relapse after radical treatment for prostate cancer. Radiol Med. 2008;113:895-904.
- Krause BJ, Souvatzpglou M, Tuncel M, et al. The detection rate of [(11) C]choline-PET/CT depends on the serum PSA-value in patients with biochemical recurrence of prostate cancer. Eur J Nucl Med Mol Imaging. 2008;35:18-23.
- Soloviev D, Fini A, Chierichetti F, Al-Nahhas A, Rubello D. PET imaging with 11C-acetate in prostate cancer: a biochemical, radiochemical, and clinical perspective. Eur J Nucl Med Mol Imaging. 2008;35:942-9.
- Vāvere AL, Kridel SJ, Wheeler FB, Lewis JL. 1-11C acetate as a PET radiopharmaceutical for imaging fatty acid synthase expression in prostate cancer. J Nucl Med. 2008;49:327-34.
- Kato T, Tsukamoto E, Kuge Y, et al. Accumulation of [(11)C]acetate in normal prostate and benign prostatic hyperplasia: comparison with prostate cancer. Eur J Nucl Med Mol Imaging. 2002;29:1492-5.
- Jadvar H. Molecular imaging of prostate cancer: PET Radiotracers. AJR Am J Roentgenol. 2012;199:278-91.
- Oyama N, Miller TR, Dehdashti F, et al. 11C-acetate PET imaging of prostate cancer: detection of recurrent disease at PSA relapse. J Nucl Med. 2003;44:549-55.
- 45. Sandblom G, Sorensen J, Lundin N, Häggman M, Malmström PU. Positron emission tomography with 11C-acetate for tumor detection and localization in patients with prostate specific antigen relapse after radical prostatectomy. Urology. 2006;67:996-1000.
- Jadvar H. PET of glucose metabolism and cellular proliferation in prostate cancer. J Nucl Med. 2016;57:25-95.
- Kwon T, Jeong IG, You D, Hong JH, Ahn H, Kim CS. Prevalence and clinical significance of incidental 18F-fluorodeoxyglucose uptake in prostate. Korean J Urol. 2015;56:288-94.
- Öztürk H, Karapolat I. 18F-fluorodeoxyglucose PET/CT for detection of disease in patients with prostate-specific antigen relapse following radical treatment of a local-stage prostate cancer. Oncol Lett. 2016;11:316-22.
- Richter JA, Rodríguez M, Rioja J, et al. Dual tracer 11C-choline and FDG-PET in the diagnosis of biochemical prostate cancer relapse after radical treatment. Mol Imaging Biol. 2010;12:210-17.
- Hillner BE, Siegel BA, Shields AF, et al. Relationship between cancer type and impact of PET and PET/CT on intended management: findings of the National Oncologic PET Registry. J Nucl Med. 2008;49:1928-35.
- 51. Afshar-Oromieh A, Malcher A, Eder M, et al. PET imaging with a [68Ga] gallium-labelled PSMA ligand for the diagnosis of prostate cancer: biodistribution in humans and first evaluation of tumour lesions. Eur J Nucl Med Mol Imaging. 2013;40:486-95.
- 52. Afshar-Oromieh A, Zechmann CM, Malcher A, et al. Comparison of PET imaging with a (68)Ga-labelled PSMA ligand and (18)F-choline-based PET/CT for the diagnosis of recurrent prostate cancer. Eur J Nucl Med Mol Imaging. 2014;41:11-20.
- Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid 68Ga-PS-MA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med. 2015;56:668-74.

- 54. Medina-Ornelas S, García-Pérez FO. Effectiveness of radiolabelled somatostatin analogues (90Y-DOTATOC and 177Lu-DOTATATE) in patients with metastatic neuroendocrine tumours: a single centre experience in Mexico. Rev Esp Med Nuc Ima Mol. 2017;36:166-74.
- Matei DV, Renne G, Pimentel M, et al. Neuroendocrine differentiation in castration-resistant prostate cancer: a systematic diagnostic attempt. Clin Genitourin Cancer. 2012;10:164-73.
- Luboldt W, Zöphel K, Wunderlich G, et al. Visualization of somatostatin receptors in prostate cancer and its bone metastases with Ga-68-DOTATOC PET/CT. Mol Imaging Biol. 2010;12:78-84.
- 57. Savelli G, Muni A, Falchi R, et al. Somatostatin receptors over-expression in castration resistant prostate cancer detected by PET/CT: preliminary report of in six patients. Ann Transl Med. 2015;3:145.



**REVIEW ARTICLE** 

### Can Omega 3 Supplements Prevent Cancer Therapy Neurocognitive Toxicity?

www.gamo-smeo.com

sociedad mexicana de oncología, a.c. GACETA MEXICANA

DE ONCOLOG

#### Santiago Vilar-González<sup>1,\*</sup> and José Luis Besteiro-González<sup>2</sup>

<sup>1</sup>Oncology Department, Queen Alexandra Hospital, Cosham, UK; <sup>2</sup>Centro Médico de Asturias, Universidad de Oviedo, Oviedo, Spain

Received for publication: 19 May 2016; accepted for publication: 25 February 2017 Available online: 10 July 2017

#### **KEYWORDS**

Neurotoxicity; Polyunsaturated fatty acid; Omega 3; Eicosapentaenoic acid; Docosahexaenoic acid; Prevention **Abstract** Therapeutics used for the treatment of cancer can generate cognitive deterioration. Any advance in the prevention of neurotoxicity would be of major importance. Omega 3, a group of polyunsaturated fatty acids, may play a prominent role in this regard. Omega 3 fatty acids exert their protective effects through multiple direct and indirect pathophysiological mechanisms. Evidence has been obtained about their use in this setting both from preclinical and clinical trials, as well as from studies on their use in other pathologies as prevalent as Alzheimer's disease and other type of dementias. This is why studies are required to confirm the hypothesis that omega 3 supplements may prevent cancer treatment-induced brain damage. (creativecommons.org/licenses/by-nc-nd/4.0/).

PERMANYER

\*E-mail for correspondence: santiagov06@gmail.com (S. Vilar-González)

http://dx.doi.org/10.24875/j.gamo.17000008

1665-9201 / © 2017 Sociedad Mexicana de Oncología. Publicado por Permanyer México. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

#### INTRODUCTION

Cancer incidence and prevalence is considerably increasing because new therapies are able to prolong cancer patients' survival, with this adding to general population aging (with possible associated cognitive deterioration). According to the Spanish Society of Medical Oncology (SEOM), cancer incidence in Spain for 2015 was expected to be 222,069 new annual cases, with a prevalence of more than 1,500,000 patients.

On the other hand, chemotherapy and hormone therapy, as well as radiotherapy to the central nervous system, generate brain damage in the form of cognitive impairment<sup>1</sup>.

This is why correct management of neurocognitive toxicity acquires more relevance. It would be interesting to have treatments available that would help to prevent and treat this toxicity. Currently, we already have a therapeutic option available in this line: memantine, a drug approved for the treatment of Alzheimer's disease (AD) that has demonstrated efficacy in the prevention of cognitive impairment caused by whole brain irradiation of brain metastases (RTOG 0614 results)<sup>2</sup>. The likelihood to develop cognitive impairment after this type of irradiation is around 34% at six months, and it increases over time according to a recent study<sup>3</sup>. Any new evidence with regard to its prevention would be of great interest.

In this line, omega 3 fatty acids (FA) may play an important role. Omega 3 FAs are a type of polyunsaturated fatty acids (PUFA), which have this name because they are not completely saturated with hydrogen atoms and, consequently, they exhibit several carbon-carbon double bonds. They are known as omega 3 because the first double bond is located three carbons prior to the last one, the omega carbon. There are also omega 6 PUFAs and omega 9 FAs (monosaturated), with olive oil (oleic acid) being their main representative in our diet (OA, C18:ln-9) (Fig. 1).

Omega 3 FAs are derived, by the action of elongases and desaturases, from alpha-linolenic acid (ALA, C18:3n-3), and omega 6 FAs from linoleic acid (LA, C18:2n-6). These enzymes introduce new carbons into the chain and generate double bonds, respectively. Both ALA and LA are essential fatty acids, i.e. they have to be ingested in the diet since the human body is unable to synthesize them. Alpha-linolenic acid can be converted into eicosapentaenoic acid



Figure 1. Types of fatty acids.

Figure 2. Main omega 3 and 6 fatty acids.

(EPA, C20;5n-3) and docosahexaenoic acid (DHA, C22:6n-3), both long-chain omega 3 FAs. However, this transformation is very limited and most EPA (90-95%) and DHA (almost 100%) are obtained from the diet<sup>4,5</sup>. Arachidonic acid (ARA, C20:4n-6), the main omega 6 FA, is also essential, although it is very abundant in animal fat (Fig. 2).

Docosahexaenoic acid is a main constituent of cell membrane phospholipids, especially in neural and retinal cells and spermatozoids, although it is also a producer of cell mediators, whereas EPA plays a more important role as a producer of cell mediators through its breakdown. The omega 3-rich foods are: fish (white but specially blue one), some dried fruits, shellfish (crustaceans and mollusks), green-leaf vegetables, some fruits such as avocado, flax, and pumpkin seeds, legumes and seed oils, especially soy, linseed, and canola oil (Fig. 3).

#### POLYUNSATURATED FATTY ACID FUNCTIONS

Omega 3 and 6 PUFAs are essential for brain development in the fetal and postnatal periods<sup>6</sup> for neuronal growth, synaptic processing, and for the expression of genes that regulate cell differentiation and growth. In addition, they are essential for the development of the retina and the visual cortex<sup>7</sup>. Especially, omega 3 FAs are crucial for the synthesis of myelin and the maintenance of adult brain structure and functionality by providing more plasticity, permeability, and fluidity to cell membranes8. Fluidity is essential for better function of the cell membrane by allowing an adequate spatial coupling between receptors and their effectors. On the other hand, fluidity also determines excitability and nervous transmission capacity of the membrane. Fatty acids and cholesterol play a relevant role in the regulation of physicochemical properties of membranes. The higher the proportion of cholesterol and saturated FAs, the higher the rigidity will be, whereas higher proportions of DHA, ARA, and oleic acid allow for the membrane to be more fluid and permeable. On the other hand, by means of phospholipase, cyclo-

SOURCES OF OMEGA 3				
Fish	Salmon, Red mullet Herring, Bonito, Tuna, Cod, Sardine, Whitebait, Anchovy, Mackerel, Dogfish, Shark, Swordfish, Trout			
Crustaceans and Mollusks	Crab, Shrimp, Clams, Lobster, Oysters, Mussels, Octopus, Squid, Cuttlefish, Sea Snails			
Dried Fruits	Nuts Pistachio			
Vegetables	Lettuce, Broccoli, Watercress, Collard, Greens, Spinach			
Fruit	Avocado			
Legumes	Grains, Beans, Peas, Soy, Oats			
Oils	Soy, Linseed, Canola			

Figure 3. Sources of omega 3.

oxygenase and lipoxygenase enzymatic action on EPA, mediators that participate in cell communication are generated. The substances resulting from enzymatic action on omega 3 and 6 PUFAs are prostaglandins, thromboxanes, and leukotrienes (eicosanoids) and new, recently discovered molecules (resolvins), whereas from EPA, eicosanoids of series 3 and 5 are obtained. From ARA, series 2 and 4 eicosanoids, with the last two showing a marked inflammatory nature. There is antagonism between omega 3 and omega 6 FAs with regard to their functions. Vasodilatation, inflammation, and coagulation, among other issues, will be affected according to their balance (Fig. 4).

This is why sufficient PUFA intake is as important as an adequate balance of omega 3 and 6 FAs since this will determine the synthesis of beneficial or noxious eicosanoids. A correct proportion between both will elicit anti-inflammatory, neuroprotective, and cardiovascular health preventive effects. The ideal dietary proportion between omega 6 and 3 FAs would be 3-4/1. If the intake of either one of them increases, the others will be proportionally reduced since both compounds compete with each other to turn into active metabolites in the body<sup>5</sup>.

In summary, PUFAs exert their multiple functions through three types of biological effects<sup>9</sup>:

Effects caused by the bioactive mediators resulting from their breakdown through phospholipase A<sub>2</sub> initial effect and the subsequent participation of an entire enzymatic cascade that generates eicosanoids and resolvins, with the latter displaying high potency at minimal doses and acting as anti-inflammatory substances or in the resolution of inflammatory processes. This is of great interest to prevent all those inflammatory phenomena that are possible precursors of the cognitive deterioration that can be caused by the use of radio- or chemotherapy<sup>10,11</sup>.

- Direct effects resulting from cell membrane ion channels (calcium, sodium and potassium) interrelation<sup>12</sup> generate anti-arrhythmic effects that are different from those of traditional anti-arrhythmic agents.
- Effects by their direct incorporation to membrane phospholipids, which generates physicochemical changes that modulate receptors and proteins, or by direct action on nuclear receptors, with both situations resulting in an action on the genome and its expression<sup>13,14</sup>.

#### OMEGA 3 AND NEUROCOGNITION

There is increasing evidence that suggests that an underlying pro-inflammatory and pro-oxidant state, favored by an



Figure 4. PUFA-derived antagonistic eicosanoids.

inadequate diet, is shared by age-related cognitive decline, Alzheimer's disease (AD), cardiovascular diseases (CVD), and cancer. Dietary lipid profile determines the composition and function of membranes, cell transmission, inflammatory processes, blood coagulability and atherogenicity, all being associated with cognitive function. The brain is one of the organs with the highest concentration of lipids (60%), especially DHA and ARA<sup>15</sup>. Although without entirely conclusive data, available evidence suggests that omega 3 FAs may play an important role in the prevention of brain damage. Evidence originating in biological and epidemiological studies indicates that reduced omega 3 PUFA intake is associated with a higher risk of dementia<sup>16-18</sup>. In animal models, dietary DHA increase delayed the expression of AD, improved cognitive performance, and decreased  $\beta$ -amyloid deposits<sup>19-21</sup>. Lower plasma and erythrocyte DHA concentrations have also been demonstrated in patients with AD<sup>22</sup>. These decreased DHA levels might be due to insufficient intake of this compound in particular, or also to reduced ingestion of monounsaturated FAs, such as oleic acid, which has been shown to be crucial for ingested DHA to fix to neuronal membrane phospholipids<sup>23</sup>. The most widely accepted theory about the cause of AD attributes the disease to abnormal deposits of  $\beta$ -amyloid and tau proteins in the brain of these patients. which produces a chronic inflammation that irreversibly damages the neurons. DHA has been shown to slow protein tau accumulation and to reduce  $\beta$ -amyloid levels, with this compound acting better alone than when administered together with omega 6 FA<sup>24</sup>. Currently, the most recent lines of investigation are focused on drugs that inhibit the production of prostaglandin E2 (PGE2) with the purpose of stopping AD chronic inflammation and  $\beta$ -amyloid accumulation<sup>25</sup>, but a more physiological alternative to stop this production could be dietary omega 3 PUFA intake.

# OMEGA 3 FATTY ACID NEUROPROTECTIVE MECHANISM

Several mechanisms have been proposed to explain omega 3 PUFAs protective function in cognitive deterioration. In the first place, they can protect by reducing the incidence of CVD and the risk for non-hemorrhagic stroke. In rebuttal of this hypothesis, a recent study that used PUFA supplements in patients with multiple cardiovascular risk factors failed to demonstrate any reduction in cardiovascular mortality and morbidity<sup>26</sup>. On the other hand, there is evidence that CVD increases the risk for dementia<sup>27-29</sup>. The benefits of long-chain PUFAs in the reduction of cardiovascular risk include the following effects<sup>9,27</sup>:

- Anti-arrhythmic effects; DHA alone or associated with EPA is a protective factor against arrhythmia and cardiac sudden death<sup>30,31</sup>;
- Anti-thrombotic effects<sup>32</sup>;
- Anti-inflammatory effects<sup>33,34</sup>;
- Anti-atherogenic effects<sup>35,26</sup>;
- Blood pressure-lowering effects<sup>37-39</sup>;
- Heart rate-lowering effects<sup>38,40</sup>;
- Endothelial function-enhancing effects<sup>41-43</sup>;
- They reduce the synthesis of pro-inflammatory cytokines, especially PGE2, interleukin 1β and tumor necrosis factor-alpha<sup>44-47</sup>;

- Other authors also indicate that PUFAs prevent glucose uptake difficulties in the aging brain, with this being a crucial factor in maintaining a good cognitive function<sup>48</sup>;
- Omega 3 FAs also reduce triglycerides (TG) hepatic synthesis, since they are poor substrates for the enzymes responsible of TG synthesis and they also inhibit other fatty acid esterification. Fatty acid  $\beta$ -oxidation increase in liver peroxisomes also contributes to TG decrease by reducing the amount of free fatty acids available for their synthesis. Inhibition of this synthesis decreases very low density lipoprotein<sup>30,49,50</sup>.

All these protective mechanisms might also prevent or avoid inflammatory phenomena caused by antineoplastic treatments<sup>51,52</sup>, and hence the interest in studying the role that omega 3 PUFAs might play in the prevention of cognitive damage in these patients.

Given that DHA is a primary component of the membrane phospholipids in the brain, adequate concentrations of omega 3 PUFA may protect against brain damage by protecting the membrane integrity and neuronal function. In animal models, dietary DHA increase has shown to facilitate neuronal membrane fluidity and excitability, to increase neurotransmitter levels, increase visual and auditory response. and reduce neuronal damage<sup>18</sup>. In behavioral models, this translated into a learning increase and higher memory performance in comparison with animals fed with control diet<sup>19,53</sup>. On the other hand, studies in animals and humans showed that an elevated caloric intake in the form of saturated FAs promotes the deposit of amyloid plagues<sup>54</sup>, whereas DHA-enriched diets decrease the accumulation of  $\beta$ -amyloid, its precursor protein, tau protein, and presenilin 1, thus protecting from dendrite  $loss^{24,54-56}$ . On the other hand, EPA can counteract ARA's vasoconstrictor effects.

The absence of conclusive data on the optimal balance of DHA and EPA is noteworthy in neurocognitive impairment and CVD prevention<sup>27</sup>.

Omega 3 FAs also act on the functioning of neuronal systems that use dopamine and serotonin. By influencing these neurotransmitters, among other aspects, brain processes that control mood and anxiety can be affected<sup>57,58</sup>.

An exhaustive review of the Cochrane Collaboration about published studies on omega 3 FA neurocognitive preventive effect does not allow for a single conclusive study to be highlighted, since all have some methodological failure. But "the sum of several omega 3 PUFAs small protective effects can constitute a significant protective effect against age-related risk for dementia and cognitive decline"<sup>59</sup>. Based on available evidence from prospective epidemiologic cohort studies on the relationship between diet and lipid intake with cognitive deterioration and dementia, it can be concluded that high intake of PUFA, monosaturated FA, and omega 3 FA is a protective factor.

There are also randomized trials in elderly people with AD and some type of established dementia with PUFA dietary supplements<sup>60-63</sup>. In all of them, an improvement in neuro-cognitive functions, such as memory or learning capacity, is demonstrated (Table 1).

With regard to age-related cognitive decline prevention, there are three randomized trials with different PUFA doses and proportions, as well as with different intervention

Study	Dose	Duration	Placebo	Tolerance	Sample
Yehuda, et al. <sup>60</sup>	Compound with 4/1 ratio between omega 6 and 3	1 month	Not described	Not described	100 pts. with AD
Terano, et al. <sup>61</sup>	0.720 g DHA	1 year	No	Not described	20 pts. with CV dementia
Freund-Levi, et al. <sup>62</sup>	1.7/0.6 g DHA/EPA	6 months	2.4 g LA (4 g corn oil)	Good	204 pts. with AD
Yurko-Mauro, et al.63	0.9 g DHA	24 weeks	50-50% corn and soy oil	Good	485 pts. with ARCD
Dangour, et al.64	0.5/0.2 g DHA/EPA	24 months	1.3 g olive oil	Good	867 pts. with ARCD
Van de Rest, et al.65	1.8 or 0.4 EPA/DHA	26 weeks	Sunflower oil	Good	302 pts. with ARCD

Table 1. Published randomized trials with omega 3 supplements in cognitive deterioration

AD: Alzheimer's disease; ARCD: age-related cognitive decline; CV: cardiovascular; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; LA: linoleic acid; pts.: patients.

periods, which have failed to demonstrate their efficacy in this topic. Only one of the three trials has demonstrated improvement in memory and learning<sup>63-65</sup>. These unfavorable results can be attributed to different reasons such as sample size, doses and used proportions, degree of baseline cognitive impairment, intervention and follow-up periods, or even the placebo employed<sup>66</sup>.

There is an ongoing three-year interventional trial on cognitive impairment prevention, which plans to recruit 1,200 cognitively healthy elderly patients. There are four arms: one with multifactorial intervention, one with multifactorial intervention, one only with omega 3, and the last one with placebo<sup>67</sup>.

An evidence-based report issued by the Agency for Healthcare Research and Quality suggested that "trials should be designed to assess omega 3 PUFA effects with the purpose to assess the effect of the omega 3 PUFA origin, dose, treatment duration, and effect maintenance after discontinuing their consumption". According to this report, "it is necessary to conduct adequately designed randomized controlled trials, with sufficient power and adequate duration (3-5-year supplementation and follow-up) with regard to dementia. These studies should include a baseline assessment on omega 3 and omega 6 PUFAs dietary consumption". Finally, the report also suggests that all studies should use standard validated instruments to assess clinical results<sup>68</sup>. Additionally, the type of fish consumed and the preparation method employed has to be taken into account in observational studies<sup>69</sup>.

Identifying randomized trials where cognitive deterioration prevention with omega 3 PUFA supplements is analyzed in cancer patients has not been possible, although, as previously showed, they might play a prominent protective role against radio- or chemotherapy related neurocognitive toxicity. With regard to the latter, the timing for initiation (before, during, or after therapy), the quantity, the proportion between PUFAs, and treatment duration might play a crucial role with regard to offering some benefit<sup>66</sup>.

Finally, it should be mentioned that interest is starting to exist in demonstrating the potential toxicity prevention and even survival improvement by using omega 3 supplements together with standard cancer therapies<sup>51,52</sup>.

#### **RECOMMENDATIONS ON OMEGA 3 DAILY INTAKE**

There is great disparity between different institutions on the recommended dietary allowance (RDA). The UK Food Standards Agency current recommendations for non-reproductive age males and females are 1-4 servings of oily fish per week, in 140 g portions. The WHO recommends omega 3 PUFA 300-500 mg daily supplements<sup>9,70</sup>. The American Heart Association (AHA) recommends EPA and DHA 1 g/day mixed supplements in all those patients with coronary disease<sup>71,72</sup>, and approximately 500 mg/day for the rest, with these figures being consistent with the International Society for the Study of Fatty Acids and Lipids recommendation<sup>27</sup>. This dose is also associated with lower risk for coronary disease-associated death, as observed in multiple epidemiological studies in the USA<sup>27,72</sup>. The consumption of two servings of oily fish per week (approx. 300 g) would provide 4.9 g of omega 3 PUFA, which is equivalent to 700 mg/day. The Spanish Society of Community Nutrition (SENC - Sociedad Española de Nutrición Comunitaria) specifies that the DHA and EPA daily intake should be 200 mg. To cover the RDA, the SENC recommends the consumption of 3-4 servings of fish and shellfish per week (one serving = 125-150 g), 3-6 tablespoons of olive oil per day (30-60 ml), and 3-7 servings of dried fruits per week (one serving = 20-30 g). In France, a DHA daily intake of 120 and 100 mg is recommended for males and females, respectively. In the USA, the National Academy of Medicine recommends an EPA and DHA intake of 100 mg/day, whereas the Technical Committee on Dietary Lipids of the International Life Sciences Institute (ILSI) recommends an EPA + DHS RDA of 250-500 mg.

Let's observe which doses have demonstrated the benefical effects of PUFAs in different situations:

- In severe inflammatory pathologies such as rheumatoid arthritis, high doses of 4-8 g/day are required<sup>73</sup>;
- Effective doses for attention deficit disorder with hyperactivity, anxiety, major depression<sup>74</sup>, bipolar disorder<sup>75</sup>, and postpartum depression seem to be around 1-2 g/day, while higher doses do not appear to be more efficacious<sup>58,76,77</sup>;
- Doses of 2-4 g are required in the prevention of  $CVD^{47,78}$ ;

- Doses of 0.5-2.0 g are necessary to obtain beneficial effects on arrhythmias<sup>27,79</sup>;
- TG anti-aggregation and reduction, especially in severe hypertriglyceridemia (> 500 mg/dl), require elevated doses of 3-4 g<sup>27,71,80</sup>.

With regard to intake recommendations, it should be noted that nutrient administration in the form of supplements does not necessarily have the same influence on the risk for dementia as the consumption of the same nutrients as part of the diet. The quality and proportions of nutrients naturally present in food have effects on absorption, metabolism, and ultimately on bioavailability, which are substantially different than would be expected with the administration of a single nutrient at pharmacological doses.

The intake of supplements will increase their concentrations, but there are non-dietary nutritional factors, such as absorption, metabolism, and genetic factors, that may affect human plasma and tissue concentration of FAs, without a proportional increase in the intake being produced<sup>81</sup>.

Finally, when assessing their bioavailability, the formulation of omega 3 supplements is crucial; there are the following presentations:

- Triglycerides (at concentrations of 70%, with this being the formulation with the highest bioavailability)<sup>5</sup>;
- In the form of ethyl or methyl esters (at concentrations between 50-70%)<sup>5</sup>;
- Or, in the form of free fatty acids9.

#### TOLERANCE TO OMEGA 3 FATTY ACIDS

The USA ILSI Lipid Technical Committee concluded in 2008 that there is no evidence that the EPA plus DHA recommended intake is harmful. On the other hand, the FDA classifies the intake of omega 3 FAs originating from fish as safe in general terms, as demonstrated in several randomized clinical trials<sup>64,65</sup>.

The observed adverse effects are basically nausea, gastrointestinal discomfort, diarrhea, and fish-smelling breath; this is why their consumption is recommended during meals.

At dosages of 20 g/day, an increase in coagulation time has been observed in healthy volunteers, without associated hemorrhagic complications<sup>27</sup>. It has been concluded that doses higher than 7 g/day, mixing DHA plus EPA, are safe even with concomitant use of warfarin or anti-aggregants<sup>9,27,82</sup>. A prolongation of coagulation time is described associated with the use of 4 g, without significant bleeding episodes being produced. As a cautionary measure, periodic monitoring of all patients taking hemostasis-altering drugs is advised, with special attention to prothrombin time, which anyway is already routine practice.

Slight increases in blood sugar have also been observed in patients with type 2 diabetes mellitus, with no changes in HbA1c levels.

On the other hand, long-term consumption of fish oil in elevated quantities can cause vitamin E deficiency, and it is therefore added to many of these commercial preparations, but regular use of vitamin E-enriched products can also lead to elevated levels of this fat-soluble vitamin with the ensuing risk of overdosing<sup>9</sup>.

#### CONFOUNDERS IN STUDIES ON COGNITIVE IMPAIRMENT PREVENTION

The ApoE gene is a pleomorphic gene with three main alleles: ApoE2, ApoE3 and ApoE4. It encodes for a protein that is essential for the catabolism of triglyceride-rich lipoproteins. This protein is the most important cholesterol transporter in the brain. ApoE proteins have been recognized for their importance in lipoprotein metabolism and in the development of CVD. The ApoE4 genotype has been associated with higher sensitivity to contract AD, to develop atherosclerosis, and to experience cognitive development deterioration. In addition, it is also associated with a lack of benefit after the consumption of PUFA-rich diets<sup>83</sup>, an observation that might explain the inconsistent results between studies and that reflects the importance of taking genetic factors into account in future studies<sup>66,84,85</sup>.

Finally, another potential confounder should be mentioned. Increased homocysteine plasma concentration is an important independent risk factor for atherosclerosis, coronary disease, death due to cardiovascular causes, stroke, dementia, and AD. Folic acid isolated administration or in combination with vitamins  $B_{12}$  and  $B_6$  can reduce its concentration<sup>86</sup>. Blood homocysteine should be determined in cognitive impairment prevention studies or all included patients should be supplemented with folic acid and vitamins  $B_{12}$  and  $B_6$ .

#### CONCLUSION

Cancer incidence and prevalence are increasing, with an increase in long-term survivors thanks to therapeutic improvements. This results in an increased risk for neurotoxicity development. Any advance with regard to its prevention will be of utmost importance. Omega 3 PUFAs may play an important role in this line. These PUFAs are a major constituent of cell membrane, and especially of neural membrane, phospholipids. They are crucial for the synthesis of myelin and maintenance of the structure and functionality of the brain. In addition, they are producers of cell mediators involved in inflammatory processes. Their mechanisms of action are mainly based on the effects caused by bioactive mediators resulting from their breakdown, which act as anti-inflammatory substances, or on inflammatory process-resolution pathways. Another important aspect is their direct incorporation to membrane phospholipids. An adequate supplementation of omega 3 PUFAs might prevent cancer treatment-related neurotoxicity. No randomized trials on this subject could be found. When conducting this type of trial, the initiation timing (before, during, or after therapy), the amount, the proportion between omega 3 PUFAs, and treatment duration might play a crucial role. In addition, genetic and physicochemical factors such as patient genotype with regard to the ApoE gene or homocysteine plasma concentration are highly important to avoid bias or confounding in the results. Interest is starting to exist in demonstrating possible toxicity prevention and even improved survival by using these types of supplements together with standard cancer therapies. In view of all that has been set forth above, well-designed studies on the use of omega 3 PUFA supplements will be able to answer many of the posed questions with regard to anti-cancer therapy related neurocognitive damage.

#### ACKNOWLEDGEMENT

The authors would like to thank Marian Torres Berruezo for her design of the figures.

#### **DECLARATION OF INTEREST**

There are no conflicts of interest relevant to the present work.

#### REFERENCES

- Heather J, Kristin P, Sari Ch, et al. Meta-analysis of cognitive functioning in Breast cancer survivors previously treated with standard-dose chemotherapy. J Clin Oncol. 2012;30:3578-87.
- Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain Radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol. 2013;15:1429-37.
- Ebi J, Sato H, Nakajima M, Shishido F. Incidence of leukoencephalopathy after whole-brain radiation therapy for brain metastases. Int J Radiat Oncol Biol Phys. 2013;85:1212-17.
- Plourde M, Cunnane S. Extremely limited synthesis of long chain polyunsaturates in adults: implications for their dietary essentiality and use as supplements. Appl Physiol Nutr Metab. 2007;32:619-34.
- Arterburn L, Hall E, Oken H. Distribution, interconversion, and dose response of n-3 fatty acids in humans. Am J Clin Nutr. 2006;83(Suppl):1467-76S.
- Bourre J. Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 1: micronutrients. J Nutr Health Aging. 2006;10:377-85.
- Rojas C, Martinez J, Flores I, Hoffman D, Uauy R. Gene expression analysis in human fetal retinal explants treated with docosahexaenoic acid. Invest Ophthalmol Vis Sci. 2003;44:3170-7.
- Bourre J. Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 2: macronutrients. J Nutr Health Aging. 2006;10:386-99.
- De Caterina R. N-3 Fatty acids in cardiovascular disease. N Engl J Med. 2011;364:2439-50.
- Fike J. Physiopathology of radiation-induced neurotoxicity. Rev Neurol. 2011;167:746-50.
- Zhou H, Liu Z, Liu J, et al. Fractionated radiation-induced acute encephalopathy in a young rat model: cognitive dysfunction and histologic findings. Am J Neuroradiol. 2011;32:1795-800.
- Anand R, Alkadri M, Lavie C, Milani R. The role of fish oil in arrhythmia prevention. J Cardiopulm Rehabil Prev. 2008;28:92-8.
- De Caterina R, Massaro M. Omega-3 fatty acids and the regulation of expression of endothelial pro-atherogenic and pro-inflammatory genes. J Membr Biol. 2005;206:103-16.
- Li Q, Wang M, Tan L, et al. Docosahexaenoic acid changes lipid composition and interleukin-2 receptor signaling in membrane rafts. J Lipid Res. 2005;46:1904-13.
- Sastry P. Lipids of nervous tissue: composition and metabolism. Prog Lipid Res. 1985;24:69-176.
- Beydoun M, Kaufman J, Satia J, Rosamond W, Folsom A. Plasma n-3 fatty acids and the risk of cognitive decline in older adults : the Atherosclerosis Risk in Communities Study. Am J Clin Nutr. 2007;77:1103-11.
- Barberger-Gateau P, Letenneur L, Deschamps V, Peres K, Dartigues J, Renaud S. Fish, meat, and risk of dementia: cohort study. BMJ. 2002;325:932-3.
- Morris M, Evans D, Bienias J, et al. Consumption of fish and n-3 fatty acids and risk of incident Alzheimer disease. Arch Neurol. 2003;60:940-6.
- Gamoh S, Hashimoto M, Sugioka K, et al. Chronic administration of docosahexaenoic acid improves reference memory-related learning ability in young rats. Neuroscience. 1999;93:237-41.

- Moriguchi T, Salem N. Recovery of brain docosahexaenoate leads to recovery of spatial task performance. J Neurochem. 2003;87:297-309.
- Lim GP, Calon F, Morihara T, et al. A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. J Neurosci. 2005;25(12):3032-3040.
- Conquer J, Tierney M, Zecevic J, Bettger W, Fisher R. Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. Lipids. 2000;35:1305-12.
- Solfrizzi V, Panza F, Torres F, et al. High monounsaturated fatty acids intake protects against age-related cognitive decline. Neurology. 1999;52:1563-9.
- Green K, Martinez-Coria H, Khashwji H, et al. Dietary docosahexaenoic acid and docosapentaenoic acid ameliorate amyloid-beta and tau pathology via a mechanism involving presenilin 1 levels. J Neurosci. 2007;27:4385-95.
- Hoshino T, Nakaya T, Homan T, et al. Involvement of prostaglandin E2 in production of amyloid-beta peptides both in vitro and in vivo. J Biol Chem. 2007;282:32676-88.
- The Risk and Prevention Study Collaborative Group. n-3 Fatty acids in patients with multiple cardiovascular Risk factors. N Engl J Med. 2013;368:1800-8.
- Lavie C, Milani R, Mehra M, Ventura H. Omega-3 polyunsaturated fatty acids and cardiovascular diseases. J Am Coll Cardiol. 2009;54: 585-94.
- He K, Song Y, Daviglus M, et al. Fish consumption and incidence of stroke: a meta-analysis of cohort studies. Stroke. 2004;35:1538-42.
- Hofman A, Ott A, Breteler M, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet. 1997;349:151-4.
- Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999;354:447-55.
- Tavazzi L, Maggioni A, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372:1223-30.
- Din J, Harding S, Valerio C, et al. Dietary intervention with oil rich fish reduces platelet-monocyte aggregation in man. Atherosclerosis. 2008;197:290-6.
- Berg A, Scherer P. Adipose tissue, inflammation, and cardiovascular disease. Circ Res. 2005;96:939-49.
- Madsen T, Schmidt E, Christensen J. The effect of n-3 fatty acids on C-reactive protein levels in patients with chronic renal failure. J Ren Nutr. 2007;17:258-63.
- Zhao G, Etherton T, Martin K, Gillies P, West S, Kris-Etherton P. Dietary alpha-linolenic acid inhibits proinflammatory cytokine production by peripheral blood mononuclear cells in hypercholesterolemic subjects. Am J Clin Nutr. 2007;85:385-91.
- Thies F, Garry J, Yaqoob P, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomised controlled trial. Lancet. 2003;361:477-85.
- Geleijnse J, Giltay E, Grobbee D, Donders A, Kok F. Blood pressure response to fish oil supplementation: metaregression analysis of randomized trials. J Hypertens. 2002;20:1493-9.
- 38. O'Keefe J, Abuissa H, Sastre A, Steinhaus D, Harris W. Effects of omega-3 fatty acids on resting heart rate, heart rate recovery after exercise, and heart rate variability in men with healed myocardial infarctions and depressed ejection fractions. Am J Cardiol. 2006;97:1127-30.
- Ventura H, Milani R, Lavie C, et al. Cyclosporine-induced hypertension. Efficacy of omega-3 fatty acids in patients after cardiac transplantation. Circulation. 1993;88:II281-5.
- Geelen A, Brouwer I, Schouten E, Maan A, Katan M, Zock P. Effects of n-3 fatty acids from fish on premature ventricular complexes and heart rate in humans. Am J Clin Nutr. 2005;81:416-20.
- Mozaffarian D. Fish, n-3 fatty acids, and cardiovascular haemodynamics. J Cardiovas Med. 2007;8(Suppl 1):S23-6.
- Din J, Newby D, Flapan A. Omega 3 fatty acids and cardiovascular disease: fishing for a natural treatment. BMJ. 2004;328:30-5.
- Goodfellow J, Bellamy M, Ramsey M, Jones C, Lewis M. Dietary supplementation with marine omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia. J Am Coll Cardiol. 2000;35:265-70.
- Akiyamaa H, Bargera S, Barnuma S, et al. Inflammation and Alzheimer's disease. Neurobiol Aging. 2000;21:383-421.

- 45. Endres S, Ghorbani R, Kelley V, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. N Engl J Med. 1989;320:265-71.
- Calder P. Immunomodulation by omega-3 fatty acids. Prostaglandins Leukot Essent Fatty Acids. 2007;77:327-35.
- Mehra M, Lavie C, Ventura H, Milani R. Fish oils produce anti-inflammatory effects and improve body weight in severe heart failure. J Heart Lung Transplant. 2006;25:834-8.
- Freemantle E, Vandal M, Tremblay-Mercier J, et al. Omega-3 fatty acids, energy substrates, and brain function during aging. Prostaglandins Leukot Essent Fatty Acids. 2006;75:213-20.
- Berger J, Moller D. The mechanisms of action of PPARs. Annu Rev Med. 2002;53:409-35.
- Huang B, Wu P, Bowker-Kinley M, Harris R. Regulation of pyruvate dehydrogenase kinase expression by peroxisome proliferator-activated receptor-alpha ligands, glucocorticoids, and insulin. Diabetes. 2002;51:276-83.
- 51. Arshad A, Isherwood J, Mann C, et al. Intravenous  $\omega\text{-}3$  fatty acids plus gemcitabine. JPEN J Parenter Enteral Nutr. 2017;41:398-403.
- Ghoreishi Z, Esfahani A, Djazayeri A, et al. Omega-3 fatty acids are protective against paclitaxel-induced peripheral neuropathy: a randomized double-blind placebo controlled trial. BMC Cancer. 2012;12:355.
- Calon F, Lim G, Yang F, et al. Docosahexaenoic acid protects from dendritic pathology in an Alzheimer's disease mouse model. Neuron. 2004;43:633-45.
- Morris M. The role of nutrition in Alzheimer's disease: epidemiological evidence. Eur J Neurol. 2009;16(Suppl 1):1-7.
- 55. Lim G, Calon F, Morihara T, et al. A diet enriched with the omega-3 fatty acid docosahexaenoic acid reduces amyloid burden in an aged Alzheimer mouse model. J Neurosci. 2005;25:3032-40.
- Oksman M, livonen H, Hogyes E, et al. Impact of different saturated fatty acid, polyunsaturated fatty acid and cholesterol containing diets on beta-amyloid accumulation in APP/PS1 transgenic mice. Neurobiol Dis. 2006;23:563-72.
- 57. Chalon S. Omega-3 fatty acids and monoamine neurotransmission. Prostaglandins Leukot Essent Fatty Acids. 2006;75:259-69.
- Rocha Araujo D, Machado M, Nardi A. What is the effectiveness of the use of polyunsaturated fatty acid omega-3 in the treatment of depression? Expert Rev Neurother. 2010;10:1117-29.
- Lim W, Gammack J, Van Niekerk J, Dangour A. Omega 3 fatty acid for prevention of dementia. Cochrane Database Syst Rev. 2006;CD005379.
- Yehuda S, Rabinovtz S, Carasso R, Mostofsky D. Essential fatty acids preparation (Sr-3) improves Alzheimer's patients quality of life. Int J Neurosci. 1996;87:141-9.
- Terano T, Fujishiro S, Ban T, et al. Docosahexaenoic acid supplementation improves the moderately severe dementia from thrombotic cerebrovascular diseases. Lipids. 1999;34(Suppl 1):S345-6.
- Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD Study. Arch Neurol. 2006;63:1402-8.
- Yurko-Mauro K, McCarthy D, Rom D, et al. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. Alzheimers Dement. 2010;6:456-64.
- 64. Dangour A, Allen E, Elbourne D, et al. Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. Am J Clin Nutr. 2010;91:1725-32.

- Van de Rest O, Geleijnse J, Kok F, et al. Effect of fish oil on cognitive performance in older subjects: a randomized, controlled trial. Neurology. 2008;71:430-8.
- 66. Cederholm T, Salem N, Palmblad J. φ-3 fatty acids in the prevention of cognitive decline in humans. Adv Nutr. 2013;4:672-6.
- Carrié I, Van Kan G, Gillette-Guyonnet S, et al. Recruitment strategies for preventive trials. The MAPT study (MultiDomain Alzheimer Preventive Trial). J Nutr Health Aging. 2012;16:355-9.
- Armstrong CL, Shera DM, Lustig RA, Phillips PC. Phase measurement of cognitive impairment specific to Radiotherapy. Int J Radiat Oncol Biol Phys. 2012;83:e319-24.
- MacLean C, Issa AM, Newberry S, et al. Effects of omega-3 fatty acids on cognitive function with aging, dementia, and neurological diseases. Evid Rep Technol Asses. 2005;114:1-3.
- Fats and fatty acids in human nutrition. Report of an expert consultation. FAO Food Nutr Pap. 2010;91:1-166.
- Kris-Etherton P, Harris W, Appel L. Omega-3 fatty acids and cardiovascular disease: new recommendations from the American Heart Association. Arterioscler Thromb Vasc Biol. 2003;23:151-2.
- Harris W, Kris-Etherton P, Harris K. Intakes of long-chain omega-3 fatty acid associated with reduced risk for death from coronary heart disease in healthy adults. Curr Atheroscler Rep. 2008;10:503-9.
- Berbert A, Kondo C, Almendra C, Matsuo T, Dichi I. Supplementation of fish oil and olive oil in patients with rheumatoid arthritis. Nutrition. 2005;21:131-6.
- Hibbeln J. Fish consumption and major depression. Lancet. 1998;351:1213.
- Stoll A, Locke C, Marangell L, Severus W. Omega-3 fatty acids and bipolar disorder: a review. Prostaglandins Leukot Essent Fatty Acids. 1999;60:329-37.
- Riediger N, Othman R, Suh M, Moghadasian M. A systemic review of the roles of n-3 fatty acids in health and disease. J Am Diet Assoc. 2009;109:668-79.
- Ross B, Seguin J, Sieswerda L. Omega-3 fatty acids as treatments for mental illness: which disorder and which fatty acid? Lipids Health Dis. 2007;6:21.
- Christensen J, Gustenhoff P, Korup E, et al. Effect of fish oil on heart rate variability in survivors of myocardial infarction: a double blind randomised controlled trial. BMJ. 1996;312:677-8.
- Ryan A, Keske M, Hoffman J, Nelson E. Clinical overview of algal-docosahexaenoic acid: effects on triglyceride levels and other cardiovascular risk factors. Am J Ther. 2009;16:183-92.
- Harris W, Ginsberg H, Arunakul N, et al. Safety and efficacy of Omacor in severe hypertriglyceridemia. J Cardiovas Risk. 1997;4:385-91.
- Sun Q, Ma J, Campos H, Hankinson S, Hu F. Comparison between plasma and erythrocyte fatty acid content as biomarkers of fatty acid intake in US women. Am J Clin Nutr. 2007;86:74-81.
- Harris W. Expert opinion: omega-3 fatty acids and bleeding-cause for concern? Am J Cardiol. 2007;99:44-6C.
- Barberger-Gateau P, Raffaitin C, Letenneur L, et al. Dietary patterns and risk of dementia: the Three-City cohort study. Neurology. 2007;69:1921-30.
- Huang T, Zandi P, Tucker K, et al. Benefits of fatty fish on dementia risk are stronger for those without APOE-epsilon4. Neurology. 2005;65:1409-14.
- Kim J, Basak J, Holtzman D. The role of apolipoprotein E in Alzheimer's disease. Neuron. 2009;63:287-303.
- Sheshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med. 2002;346:476-83.



#### **REVIEW ARTICLE**

# Health Economic Assessment: Applications, Rationale, Methodology and Common Mistakes

SOCIEDAD MEXICANA DE ONCOLOGÍA, A.C. GACETA MEXICANA

DE ONCOLOGI

www.gamo-smeo.com

#### **Eleanor Saunders\***

Health Economics and Policies Consultant

Received for publication: 23 June 2016; accepted for publication: 25 February 2017 Available online: 10 July 2017

#### **KEYWORDS**

Cost-effectiveness: Cost-minimization; Panitumumab; Bevacizumab; Cetuximab; Methodology; **Decision makers** 

Abstract Economic assessments are useful to compare the effects and costs of different health interventions, with the purpose to determine the best alternative for resource distribution in health institutions. To this end, it is highly important for the economic analysis to be consistent with the context where it is carried out, and to follow the established methodology on the subject. Using as an example a recently published cost-effectiveness analysis that compares panitumumab with bevacizumab and cetuximab in patients with metastatic colorectal cancer in Mexico, we will show how to develop a transparent, fair, and useful economic assessment for decision makers. (creativecommons.org/licenses/by-nc-nd/4.0/).

PERMANYER

\*E-mail for correspondence: saundersconsultingmx@gmail.com (E. Saunders)

http://dx.doi.org/10.24875/j.gamo.17000009

1665-9201 / © 2017 Sociedad Mexicana de Oncología. Publicado por Permanyer México. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

#### INTRODUCTION

Economic assessments of new treatments are primarily intended to serve as a tool for decision makers and to advise them in establishing the best alternative for resource distribution. To accomplish this goal, as well as to arrive to valid conclusions, following an established methodology is required, especially focusing on the context where the analysis takes place. Otherwise, what would be the use of an economic assessment? Based on the article by Vargas, et al. entitled "Cost-effectiveness analysis of panitumumab + FOLFOX in RAS-WT mCRC" published the Gaceta Mexicana de Oncología<sup>1</sup>, the present article outlines the fundamentals to conduct and analyze a health economic assessment, describes mistakes to be avoided, and offers tools for findings to be interpreted and validity of conclusions to be evaluated.

The fundamentals of new treatments economic assessment can be summarized in six simple points:

- Establishing a clear, precise research question;
- The research must have objectives that are consistent with the guidelines established within the context where the drugs are assessed;
- The type of economic assessment (cost-effectiveness or cost-minimization) should be justified by available evidence from quality clinical trials;
- The clinical trials used to support the effectiveness of all treatments should correspond to the study population;
- The costs used in the study should correspond to the perspective of the study, to the usual costs of a patient with a given disease, as well as to the medication, including costs of administration, hospitalization, follow-up and treatment of adverse effects; and

The sources of data on efficacy, costs and assumptions should be clearly cited and available to assessors<sup>2</sup>.

Each one of these points will be next examined in the context of the economic assessments carried out by Vargas, et al. in order to determine the methodological validity and the results of the two presented analyses: a cost-effective-ness analysis comparing bevacizumab with panitumumab and a cost-minimization analysis where cetuximab is compared with panitumumab.

### ESTABLISHING A CLEAR, PRECISE RESEARCH QUESTION

The research question is essential in order to focus the investigation and define its scope. In the analyzed article<sup>1</sup>, the research question clearly establishes the context: "Does the use of panitumumab + FOLFOX as first-line treatment in patients with wild type (WT) RAS metastatic colorectal cancer (mCRC) have an inferior cost-effectiveness ratio average versus bevacizumab + FOLFOX, as assessed from the perspective of public health institutions in Mexico?". With this question, the treatments under investigation (panitumumab and bevacizumab), the population of interest (patients with WT RAS mCRC) and the specific context (public health institutions in Mexico) are known.

For the performance of any economic assessment study, and in order for it to meet its purpose, i.e. to guide the decision maker, the assessing entity acceptance criteria, which are determined by the context itself, should be applied. In particular, for public sector institutions in Mexico, these criteria are dictated by the General Public Health Council (CSG - Consejo de Salubridad General), which is the body responsible for assessment and inclusion of new technologies into the Basic Formulary and Medication Catalogue<sup>3</sup>.

#### THE RESEARCH MUST HAVE OBJECTIVES THAT ARE CONSISTENT WITH THE GUIDELINES ESTABLISHED WITHIN THE CONTEXT WHERE THE DRUGS ARE BEING ASSESSED

#### Presentation of results

The Guidelines for the Conduction of Economic Assessment Studies for the Basic Formulary and Catalogue of Supplies of the Health Sector in Mexico Update<sup>2</sup> indicate that the presentation of a cost-effectiveness analysis (CEA) is "indispensable", with efficacy results expressed in "natural units such as, for example, life-years gained" (p. 34), and final results expressed as "incremental cost per additional efficacy unit" (p. 20). This methodology is, in addition, consistent with other reference institutions in health economic assessment at the international level<sup>4,5</sup>. However, Vargas, et al. present the results as a "cost-effectiveness average" measurement, which is not a commonly employed cost-effectiveness measure and, given the context, it doesn't allow for the decision maker to clearly know the incremental cost per efficacy unit.

The CSG establishes cost-effectiveness threshold at one GDP per capita, which is equal to MXP  $$120,214.18^{6.7}$ .

Gross domestic product per capita is calculated with the following formula:

Using Vargas, et al. own data on costs and effectiveness<sup>1</sup>, the calculation of the incremental cost-effectiveness ratio (ICER) for panitumumab in comparison with bevacizumab would be:

	(Treatment A Cost-Treatment B Cost	.)
	(Treatment A Effectiveness —Treatment B Effectiveness)	
ICER = -	(\$1,048,009.42-\$872,201.70)	
	(3.47 years-2.80 years)	\$202,377.J

According to this result, panitumumab ICER is above the cost-effectiveness threshold established for Mexico. Notwithstanding, the result presented by the author omits this information and appears to suggest the opposite by indicating that panitumumab has a lower "cost-effectiveness average ratio" than bevacizumab. The use of ICER implies acceptance by the government to pay an additional amount established for medications that demonstrate higher effectiveness. In contrast, the use of the cost-effectiveness average ratio implies that treatments with higher effectiveness should have the same cost per lifeyear gained than the other compared medications, which has at least three methodological flaws:

- It implies that new products require having the same cost per life-year gained than generic products.
- Each disease is likely to have a different life-year cost, since there is no consensus on life-year gained average cost standardization.
- This methodology is used to compare treatments against "no intervention"<sup>8</sup>.

To be correctly employed, an analysis of panitumumab versus the no intervention alternative should be included.

Cost-effectiveness analysis methodology should be consistent with the context and the guidelines where the study is developed. In this case the methodology employed by Vargas, et al. to justify panitumumab cost-effectiveness versus bevacizumab does not correspond to standard methodology, which can lead to wrong decision making in resource optimization.

#### Data on resection

It is important for sources of the data used in the economic model to be consistent with the context where it is developed. Vargas, et al. rely on data of the PEAK clinical trial to model the compared treatments efficacy. However, to model the resection, the investigators chose to rely on data of an expert panel to determine the resection rate and intervention rate of success. The CSG Guidelines clearly state: "In no case will be expert opinions able to replace proven scientific evidence"2 (p. 21). The data on resection attempt and rate of success of Vargas' analysis, 11 and 80%, respectively, for panitumumab, and 22.2 and 71%, respectively, for bevacizumab, not only considerably differ from the PEAK trial data (13.6 and 66.7% vs. 11 and 77.8%, respectively)<sup>9</sup>, but also favor panitumumab by adding the costs of unsuccessful surgery to bevacizumab-treated patients.

It is important to emphasize that actually, these data cited by Vargas, et al. do not come directly from the PEAK analysis report<sup>9</sup>, but from an economic assessment published in 2014 that was carried out by the PEAK trial sponsors, who had access to patient-level data<sup>10</sup>.

It is explained that two additional scenarios were used to determine with more certainty the validity of the results presented with the base case: "with the first one assuming the same percentages reported in the PEAK trial (13.6% for resection attempt and 66.7% for rate of success with panitumumab and 11% for resection and 77.8% for success with bevacizumab), and the second assuming no metastatic site resection is performed (0% of attempts)"<sup>1</sup> (p. 253).

However, the results of these are not presented in the article, casting more doubt on the transparence and validity of the study. In this example, unpublished data are used that justify adding more surgeries with less effectiveness to bevacizumab patients, which increases the cost of treatment for these patients, thus favoring panitumumab. Here, the recommendation would be using published data, and justify any variable value change in order for results to be replicable.

#### THE TYPE OF ECONOMIC ASSESSMENT (COST-EFFECTIVENESS OR COST-MINIMIZATION) SHOULD BE JUSTIFIED BY AVAILABLE EVIDENCE FROM RANDOMIZED CLINICAL TRIALS AT LEAST MEETING MINIMUM QUALITY REQUIREMENTS (JADAD SCALE OR CONSORT)

The researchers should choose a type of economic assessment according to available clinical information on the different comparators included in the evaluation. In the Mexican context, researchers usually choose between a cost-effectiveness analysis when the treatments to be compared have different efficacy, and a cost-minimization analysis only in cases where there is proof that there is no effectiveness difference between the drugs to be compared<sup>2</sup>.

The cost-effectiveness analysis is based on overall survival data of the PEAK trial, which compared panitumumab and bevacizumab (41.3 vs. 28.9 months, respectively). The clinical trial is completed with a statistical analysis of results to determine the 95% confidence intervals (CI) and, by this means, the certainty of the trial results. In the case of the PEAK trial, data are not statistically significant (95% CI: 0.39-1.02; p = 0.058)<sup>4</sup>. In addition, the CI is so broad that it does not allow for conclusions on the intervention effect to be extracted.

#### THE CLINICAL TRIALS USED TO SUPPORT THE EFFECTIVENESS OF ALL TREATMENTS SHOULD CORRESPOND TO THE STUDY POPULATION

Clinical trials are intended to determine the efficacy of a treatment in a specific population. For this reason, it is very important for the population where the economic assessment is carried out to correspond to this same population. In the reviewed article<sup>1</sup>, the study is carried out in patients with KRAS-WT mCRC on first-line treatment. The cost-minimization analysis between panitumumab and cetuximab is based on the assumption that both drugs have the same efficacy in the study population and, consequently, only the costs are compared, without effectiveness being considered. The author cites as clinical evidence a study in RAS-WT population on third-line therapy (the ASPECCT trial<sup>11</sup>), which is not valid to demonstrate panitumumab and cetuximab equivalence at first-line, and since a comparison merely based on costs is not justified, no valid conclusions can therefore be obtained from this analysis. In order for valid conclusions on the cost-effectiveness of these products to be presented, an analysis is required on the clinical benefits of the medications, and not only on their costs, as well as sensitivity analyses to be included to assess the impact of uncertainty on the results.

#### THE COSTS USED IN THE STUDY SHOULD CORRESPOND TO THE USUAL COSTS OF A PATIENT WITH THE DISEASE OF INTEREST, AS WELL AS TO THE MEDICATION, INCLUDING COSTS OF ADMINISTRATION, HOSPITALIZATION, OUTPATIENT CONSULTATIONS, AND TREATMENT OF ADVERSE EVENTS

In order for it to really be a tool to support decisions, the economic assessment and treatment algorithm of the average patient should adhere as much as possible to the reality where the model is developed. In addition to the aforementioned methodological points, there is an inconsistency between the two economic analyses presented in the article by Vargas, et al.<sup>1</sup> that turns out favoring panitumumab cost estimate. In the cost-effectiveness analysis of panitumumab with bevacizumab, an average patient weight of 67 kg was used based on an article<sup>12</sup> where patients with cancer were assessed at the Hospital General de México. Conversely to this data, Vargas, et al. changed patient weight to 65 kg in the comparison with cetuximab. The panitumumab dose is indicated in mg/kg, as with bevacizumab, while cetuximab dose is indicated in mg/m2. The subtle patient weight change allows for one less panitumumab vial to be used, which decreases its treatment cost, thus generating a bias in the presented results.

#### THE SOURCES OF DATA ON EFFICACY, COSTS, AND ASSUMPTIONS SHOULD BE CLEARLY CITED AND BE ACCESSIBLE TO ASSESSORS

The validity of an economic assessment is based on the quality and certainty of the employed information. For this reason, when developing a study it is important to make sure that the data are consistent with the context they are applied to, and that the sources of the analysis key data (efficacy and costs) are accessible in order to validate the model. As the authors of the article note<sup>1</sup>: "The performance of a pharmacoeconomic analysis that turns out being relevant to the national context is determined by the quality of the information it feeds on and by the consistency of the assumptions employed in the assessment model with clinical practice in Mexico"<sup>1</sup> (p. 253). In spite of this accurate statement, the same authors include non-supported assumptions or fail to mention results that are critical to the results interpretation.

When the article by Vargas, et al.<sup>1</sup> and the sources referred to justify the assumptions for costs and efficacy of the included treatments were reviewed in detail, an economic assessment was found of the PEAK clinical trial of panitumumab compared with bevacizumab<sup>9</sup>, the results of which were used as the basis for the economic assessment<sup>10</sup>. Economic models adaptation for different contexts is common practice. However, not citing the original document is considered a serious offense within the scientific community.

Overall, there is a lack of transparency in cost assumptions: How was the cost of metastasis resection estimated? Why does the range of the sensitivity analysis for this variable go from -20 to +50%? Why is the cycle number upper

range 21.65, and where does this figure come from? Why is comparator total treatment cost not reported in the cost-effectiveness analysis including administration and follow-up? All these data should be more clearly presented in order for the reader to be able to draw his/her own conclusions.

In spite of having a previously published economic assessment, these doubts are not clarified. On the contrary, some of the explained and most conservative variables in the model by Graham, et al. do not correspond to those used by Vargas, et al., where data sources are not explained. For example, the average number of treatment cycles corresponds to the average time the patient is on progression-free survival. Using parametric modeling, Graham, et al. explain that the Weibull distribution was used to define the time average the patient spends on progression-free status (19.42 cycles with panitumumab and 14.10 with bevacizumab)<sup>10</sup>. Vargas, et al. use the same number of cycles for bevacizumab (14.10), but reduce the cycles of panitumumab treatment to 18.20<sup>1</sup>. In both cases, the provenance of these data is not explained.

#### CONCLUSION

Economic assessment is a highly useful tool to compare different health technologies and to support decision makers on the use of more cost-effective treatments. Therefore, it is important to follow published methodologies that have been gradually defined with this discipline's growth. In addition to clearly explaining the study population, the technologies to be compared and the sources of data, it is important for data to be transparently used in order to prevent bias in the results.

The economic assessments of panitumumab versus bevacizumab and cetuximab presented in the article in question<sup>1</sup> involve several methodological flaws that do not allow for decision makers to determine the most adequate resource distribution option. In addition, the cost-effectiveness analysis versus bevacizumab is characterized by lack of transparency in the acquisition of data instead of being based on available scientific evidence.

With regard to the analysis versus cetuximab, an emphasis is made on the difference between the populations in the reviewed article (RAS-WT first line) and in the clinical analysis used to justify the study (KRAS-WT third line). Therefore, in addition to displaying serious methodological doubts, the cost-minimization exercise does not allow for decision making on allocation of resources for patients with mCRC on first line to be supported.

To design a serious analysis that supports decision making on resource distribution, a new model adhering to the CSG methodology would be recommended, since that is the context the study refers, as well as increasing the transparency of the sources of information. In addition, redrawing the methodology is recommended in order to present conservative results towards the treatment of interest and to promote the validity and objectivity of the study.

#### DECLARATION OF INTEREST

Eleanor Saunders declares having received financing from Merck S.A. de C.V. for the development of this article.

#### REFERENCES

- Vargas Valencia JJ, Alva Esqueda ME. Análisis de costo-efectividad de panitumumab + FOLFOX en CCRm RAS-WT. Gaceta Mex Oncol. 2015; 14:251-8.
- Consejo de Salubridad General. Guía para la Conducción de Estudios de Evaluación Económica para la Actualización del Cuadro Básico y Catálogo de Insumos del Sector Salud en México. Consejo de Salubridad General, México, 2015. Available at: www.csg.gob.mx/descargas/ pdfs/2015/GCEEE\_2015.pdf.
- Consejo de Salubridad General. Cuadro Básico y Catálogo de Medicamentos Edición 2015. Consejo de Salubridad General, México, 2015.
- Ramsey SD, Willke RJ, Glick H, et al. Cost-Effectiveness Analysis alongside clinical trials II - An ISPOR Good Research Practices Task Force Report. Value Health 2015;18:161-72.
- NICE. Assessing Cost Effectiveness. 2012. Available at: https://www. nice.org.uk/article/pmg6/chapter/7-assessing-cost-effectiveness#modelling-approaches. (Accessed 14 June 2016).
- INEGI 2015. Available at: http://cuentame.inegi.org.mx/poblacion/ habitantes.aspx?tema=P. (Accessed 8 MAy 2016).
- INEGI. Producto Interno Bruto, 2016. Available at: http://www.inegi. org.mx/est/contenidos/proyectos/cn/pibt/default.aspx. (Accessed 14 June 2016).

- Glick. Cost-Effectiveness Analysis 2012. Available at: http://www. uphs.upenn.edu/dgimhsr/documents/1b.introcea.fda12.pdf. (Accessed: 14 June 2016).
- Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: A randomized, multicenter phase II Study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wildtype KRAS Exon 2 metastatic colorectal. J Clin Oncol. 2014;32: 2240-56.
- Graham C, Hechmati G, Hjelmgren J, et al. Cost-effectiveness analysis of panitumumab plus mFOLFOX6 compared with bevacizumab plus mFOLFOX6 for first-line treatment of patients with wild-type RAS metastatic colorectal cancer. Eur J Cancer. 2014;50:2791-801.
- Price TJ, Peeters M, Kim TW, et al. Panitumumab versus cetuximab in patients with chemotherapy-refractory wild-type KRAS exon 2 metastatic colorectal cancer (ASPECCT): a randomised, multicentre, open-label, non-inferiority phase 3 study. Lancet Oncol. 2014;15: 569-79.
- Fuchs Tarlovsky V, Gutiérrez Salmeán G. Situación nutricional en pacientes oncológicos internados en un hospital public. Rev Cubana Med. 2008;47.
- Consejo de Salubridad General, 2012. Misión. Available at: http:// www.csg.gob.mx/contenidos/mision.html. (Accessed 27 May 2016).



CLINICAL CASE

# Paratesticular Desmoplastic Tumor: Case Report and Review of Literature

#### Jorge Martínez-Cedillo<sup>1,\*</sup>, Rossio Medina-Barrionuevo<sup>2</sup> and Gregorio Chanona Vilchis<sup>3</sup>

sociedad mexicana de oncología, a.c. GACETA MEXICANA

www.gamo-smeo.com

DE ONCOLOG

<sup>1</sup>Department of Medical Oncology, <sup>2</sup>Medical Oncology Resident and <sup>3</sup>Department of Pathology; Instituto Nacional de Cancerología, Mexico City, Mexico

Received for publication: 10 June 2016; accepted for publication: 25 February 2017 Available online: 10 July 2017

KEYWORDS Paratesticular desmoplastic tumor; Multimodal treatment Abstract Desmoplastic small round blue cell tumor is a rare neoplasm of the mesenchymal tissue. It occurs in adolescents and young adults with a median age of 22 years. Characteristically, it affects the intra-abdominal area, although other locations, including the paratesticular area, have been described in recent years. Usually, it has an aggressive clinical evolution with multiple recurrences, invasion to adjacent structures, and distant metastasis. **Case presentation:** We report the case of a 23-year-old male with symptoms of pain and testicular volume enlargement who underwent radical right orchiectomy with pathology report of desmoplastic small round blue cell tumor. He received intravenous chemotherapy with the vincristine, Adriamycin, cyclophosphamide/ifosfamide and etoposide regimen for 17 courses, with subsequent recurrence at the inguinal and retroperitoneal level, and surgery plus postoperative radiotherapy was therefore carried out. At the conclusion of radiotherapy, he progressed at the systemic, pulmonary, and hepatic levels and died due to multiple organ failure. (creativecommons.org/licenses/by-nc-nd/4.0/).

PERMANYER

\*E-mail for correspondence: jorge\_martinezcedillo@yahoo.com.mx (J. Martínez-Cedillo)

http://dx.doi.org/10.24875/j.gamo.17000010

1665-9201 / © 2017 Sociedad Mexicana de Oncología. Publicado por Permanyer México. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

#### INTRODUCTION

Desmoplastic small round blue cell tumor is a rare and highly aggressive neoplasm of the mesenchymal tissue. It occurs in adolescents and young adults with a median age of 22 years<sup>1</sup>. Typically, it develops in the abdominal cavity (95%), whereas only 5% occurs in other sites, including the paratesticular region<sup>2</sup>. It is a highly aggressive neoplasm, with clinical evolution characterized by multiple recurrences, invasion to adjacent structures, and distant metastasis, mainly to the lymph nodes and the lung<sup>1</sup>.

We present the case of a patient with a desmoplastic paratesticular tumor treated with multimodal therapy where an aggressive course of disease was observed.

#### CASE PRESENTATION

This is the case of a 23-year-old male patient with a history of smoking since 16 years of age at a rate of three cigarettes per day and social alcoholism. He had a one-month history of progressive right testicular enlargement associated with pain. Testicular ultrasound revealed a tumor of solid appearance on the right hemiscrotum, separated from the testis (paratesticular). Laboratory tests reported Hb: 17.6, WBC: 6,300, platelets: 301,000, LDH: 312 IU/l, AFP: 1.6 ng/ml, HCG: 0 mIU/l.

The patient underwent right radical orchiectomy and inguinal exploration, with findings of a paratesticular tumor of approximately 7 x 5 cm, rock-hard in consistency, and with irregular borders, involving the spermatic cord and its elements, in addition to right testicle upper pole. The histopathological report corresponded to a desmoplastic small round blue cell tumor of the spermatic cord; surgical margins were negative. Immunohistochemistry showed positivity to vimentin and WT-1; positivity to NSE, desmin, CD56 and Bcl-2; and negativity to ALK-1, chromogranin, myeloperoxidase and S100 (Figs. 1 and 2).

Chest, abdomen and pelvic CT scan showed no distant disease.

Adjuvant treatment was then started with intravenous chemotherapy based on Ewing's sarcoma-extrapolated VAC/IE



Figure 1. Light microscopy.



Figure 2. Immunohistochemistry study.

regimen, with vincristine 2 mg/m<sup>2</sup> (maximum dose, 2 mg), doxorubicin 75 mg/m<sup>2</sup>, cyclophosphamide 1,200 mg/m<sup>2</sup>, actinomycin D 1.25 mg/m<sup>2</sup> (when the Adriamycin dose of 375 mg/m<sup>2</sup> was reached) and ifosfamide at 1,800 mg/m<sup>2</sup> plus etoposide at 100 mg/m<sup>2</sup> every three weeks for a total of 17 courses (49 weeks).

Disease control studies after treatment were negative. At three months' follow up, there was recurrence at the retroperitoneum and right groin (Figs. 3 A and B).

Right inguinal tumor resection plus right iliac vein grafting was performed, with findings of a 15 x 8 x 6 cm tumor infiltrating the superficial tissue and fascia and spreading towards the Retzius space, with infiltration to the right external iliac artery and vein: unresectable retroperitoneal tumor. The pathology report classified it as a desmoplastic small round blue cell tumor. The patient then underwent radiotherapy (RT) to the inguinal and retroperitoneal region at 50 Gy in 25 sessions. At the conclusion of RT, a subcutaneous nodule was discovered in the mesogastrium; the control computed tomography (CT) scan showed multiple lung and liver metastases (Figs. 4 A and B). The patient evolved with multiple organ failure and died.

#### **REVIEW OF LITERATURE**

Among intrascrotal masses, paratesticular tumors account for barely 2%, as opposed to testicular tumors, which account for 98% of cases. The vast majority of paratesticular tumors (70%) are of benign etiology, among which lipoma (66%), adenomatoid tumor, leiomyoma, and fibroma are predominant. Thirty percent are of malignant etiology, out of which 90% correspond to sarcomas, with the most common being leiomyosarcoma (32%), followed by rhabdomyosarcoma (24%), and liposarcoma (20%)<sup>3,4</sup>. Paratesticular tumors are characterized by slow and painless growth. This neoplasm is more common in male adults between the second and fifth decades of life. It can affect the testicular tunics, the spermatic cord and the epididymis, with the latter being the site of higher occurrence<sup>5</sup>. Desmoplastic small round blue cell tumor is a rare and highly aggressive malignant ne-



Figure 3. A: The arrow shows retroperitoneal lymph node cluster.



Figure 4. A: Lung metastases are observed.



Figure 3. B: The arrow shows right groin lymph node cluster.



Figure 4. B: Liver metastases.

oplasm of the mesenchymal tissue. It was first described in 1989 by Gerald and Rosai. It occurs in adolescents and young adults with a median age of 22 years. The male-to-female ratio is  $4:1^{6,7}$ .

It typically develops in the abdominal cavity (95%), while only 5% occur in other sites, including the paratesticular region, pancreas, retro-orbital region, cranial cavity, lung, head and neck, and salivary glands<sup>8</sup>.

Desmoplastic tumor is considered to be a member of the childhood small round blue cell tumors family together with primitive neuroectodermal tumor (PNET), alveolar and embryonic rhabdomyosarcoma, poorly-differentiated synovial sarcoma, and rhabdoid tumors. Therefore, there is no appropriate classification system for it<sup>2</sup>.

These tumors are typically characterized by an association with the t(11;22) (p13;q12) translocation, which involves WT1 and EWSR1 genes<sup>4,6</sup>.

Most of these tumors remain asymptomatic until diagnosis. In advanced cases, clinical presentation involves ascites, pain, vomiting, and weight loss.

These are highly aggressive tumors with median survival of less than 12 months without treatment. They have a clinical course characterized by multiple recurrences, invasion to adjacent structures, and distant metastases, mainly to lymph nodes and lungs<sup>1</sup>. Differential diagnosis of this entity is mainly with Ewing's sarcoma/PNET, which can show positivity to keratins in frozen sections, but in paraffin-embedded sections, Ewing's sarcoma/PNET is characterized by positivity to CD 99 and vimentin, and negativity to cytokeratins and muscle markers. The t(11;22)(q24;q12) chromosomal reciprocal translocation in Ewing's sarcoma/PNET involves chromosome 11 long arm, unlike the translocation observed in desmoplastic tumor, which involves chromosome 11 short arm<sup>1</sup>.

With regard to treatment, the literature mentions that, owing to the t(11;22) translocation, these tumors can be treated as Ewing's sarcoma, with multimodal therapy with surgery, radiotherapy, and chemotherapy being recommended, and median survival of 17-25 months being reached with this treatment, with less than 20% survival at five years<sup>9,10</sup>.

In an extensive literature review, only few cases of small round blue cell tumors with paratesticular localization have been reported. The largest series reports only 13 cases, two of them with lung metastases at diagnosis, and four with retroperitoneal and inguinal and cervical chain lymph node metastases, with median survival of 16 months with multi-modal treatment<sup>6,11-13</sup>.

In a retrospective analysis of patients treated at the Memorial Sloan Kettering Cancer Center from July 1972 to July 2003, 66 patients with abdomen- or pelvis-located tumors (96%) and with other tumor sites (2% testis, 2% thoracic cavity), 50% with regional lymph node metastasis and 41% with distant metastasis, were treated with multimodal therapy: seven courses of VAC/IE, followed by surgery and consolidation RT at a dose of 30 Gy. Myeloablative chemotherapy with carboplatin followed by autologous transplantation was carried out in 16 patients who failed to respond to the above-mentioned therapy<sup>5</sup>. The results of this retrospective analysis show that a three-year overall survival of 44% is reached with multimodal therapy<sup>5</sup>.

The presented case is worth mentioning owing to the extreme rarity of presentation and torpid evolution, which ended in the patient dying even after aggressive multimodal therapy.

#### CONCLUSION

Desmoplastic tumor is an extremely rare and highly aggressive neoplasm. The low frequency of its occurrence makes for treatment guidelines to be based on generally retrospective experiences of several groups with individualized treatments, and the results are therefore not comparable, with multiple controversies being generated.

#### DECLARATION OF INTEREST

The authors did not receive any funding to carry out this article. The authors declare not having any conflicts of interests.

#### REFERENCES

- Brindis M, Villalobos A, de León B, et al. [Desmoplastic Tumor of Small and Round Cells. Multi-Institutional Study. Clinicopathological and Immunohistochemistry of 8 Cases.] Cancerología. 2007;2:67-74.
- Stuart-Buttle CE, Smart CJ, Pritchard S, Martin D, Welch IM. Desmoplastic small round cell tumour: a review of literature and treatment options. Surg Oncol. 2008;17:107-12
- García-González J, Villanueva C, Fernández-Aceñero MJ, Paniagua P. Paratesticular desmoplastic small round cell tumor: case report. Urol Oncol. 2005;23:132-4.
- Dufresne A, Cassier P, Couraud L, et al. Desmoplastic small round cell tumor: current management and recent findings. Sarcoma. 2012;2012:714986.
- Lal DR, Su WT, Wolden SL, Loh KC, Modak S, La Quaglia MP. Results of multimodal treatment for desmoplastic small round cell tumors. J Pediatr Surg. 2005;40:251-5.
- Gerald W, Haber DA. The EWS-WT1 gene fusion in desmoplastic small round cell tumor. Semin Cancer Biol. 2005;15:197-205.
- Roganovich J, Bisogno G, Cecchetto G, D'Amore ES, Carli M. Paratesticular desmoplastic small round cell tumor, review of the literature. J Surg Oncol. 1999;71:269-72.
- Caballero Mora FJ, Muñoz Calvo MT, García Ros M, et al. [Testicular and paratesticular tumors during childhood and adolescence]. An Pediatr (Barc). 2013;78:6-13.
- Melo M, Rodrigues R, Varela J, Lopes T. Desmoplastic tumor of vaginal tunica. Description of a clinical case and review of the literature. Acta Urológica. 2005;3:37-41
- 10. Balamuth NJ, Womer RB. Ewing's sarcoma. Lancet Oncol. 2010;11:184-92.
- Cliteur VP, Szuhai K, Baelde HJ, van Dam J, Gelderblom H, Hogendoorn PC. Paratesticular desmoplastic small round cell tumour: an unusual tumour with an unusual fusion; cytogenetic and molecular genetic analysis combining RT-PCR and COBRA-FISH. Clin Sarcoma Res. 2012;2:3.
- Yue X, Wang JZ, Tian Y, Wang KJ. Paratesticular desmoplastic small round cell tumor with metastasis: a report of two cases. Kaohsiung J Med Sci. 2014;30:104-5.
- He L, Wen S, Hu X, Guo C, Yi C. Primary desmoplastic small round cell tumor of the testis: A case report and review of the literature. Oncol Lett. 2013;6:565-7.



CLINICAL CASE

### SOCIEDAD MEXICANA DE ONCOLOGÍA, A.C. GACETA MEXICANA DE ONCOLOGÍA WWW.gamo-smeo.com



### Medullary Thyroid Cancer Metastatic to the Oral Cavity: Clinical Case

#### Luis Cruz-Benítez<sup>1,\*</sup>, Angélica Julián-Castrejón<sup>2</sup> and Juan de Dios Pérez-Reyna<sup>3</sup>

<sup>1</sup>Department of Surgical Oncology and <sup>2</sup>Department of Maxillofacial Surgery, HRAEI, SS, Ixtapaluca, Mexico; <sup>3</sup>General Surgery 4th Year Resident, Hosp. Gral. Dr. Darío Fernández Fierro, ISSSTE, Mexico City, Mexico

Received for publication: 11 November 2016; accepted for publication: 25 February 2017 Available online: 10 July 2017

#### **KEYWORDS**

Medullary cancer; Papillary cancer; Total thyroidectomy; Radical neck resection; Metastasis Abstract Medullary thyroid cancer is a neoplasm of the C cells, the function of which is to regulate calcium metabolism. It has a low incidence rate, accounting for 5% of all thyroid cancers. Its occurrence is usually sporadic (84%) or hereditary (16%), with the latter occurring within the context of familial medullary thyroid cancer or multiple endocrine neoplasia type 2, which is associated with different mutations of the proto-oncogene RET 4. It is character-ized by secreting calcitonin, which is a useful marker for staging, residual disease detection, and long-term patient follow-up. It is a relatively aggressive neoplasm since despite its slow progression, 60-80% of cases have lymph node metastases at diagnosis, which hinders fully curative therapy since more than 50% of patients have been observed to maintain elevated calcitonin levels after the first surgery. Patients with the hereditary form tend to be younger and to experience more aggressively evolving disease, with cancer often being multifocal and bilateral. The first line of therapy is surgery. (creativecommons.org/licenses/by-nc-nd/4.0/).

\*E-mail for correspondence: crubeluis@gmail.com, crubeluis@yahoo.com.mx (L. Cruz-Benítez)

http://dx.doi.org/10.24875/j.gamo.17000011

1665-9201 / © 2017 Sociedad Mexicana de Oncología. Publicado por Permanyer México. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

#### INTRODUCTION

A large variety of lesions, either malignant or benign, may cause thyroid nodules. Therefore, any patient with this condition should be investigated with regard to family history of benign or malignant thyroid disease (medullary thyroid cancer, multiple endocrine neoplasia type 2, familial papillary thyroid tumors, polyposis coli, Cowden disease, Gardner syndrome and Carney complex)<sup>1</sup>. A thyroid nodule is defined as the presence of one or more focal lesions, either palpable or visible by imaging studies, and that differ from the structure of thyroid parenchyma<sup>1</sup>.

Medullary thyroid carcinoma (MTC) was identified in 1959 by Hazard, et al., who described a variety of solid, non-follicular thyroid cancer, with a stroma rich in amyloid substance and high incidence of lymph node metastases. In 1967, Williams and Brewer described that MTC originates in parafollicular cells (C cells) of the thyroid gland. One year later, Neher demonstrated that this tumor secretes thyrocalcitonin<sup>3,4</sup>.

Medullary thyroid cancer (MTC) is a neoplasm of calcitonin-producing C cells, the function of which is to regulate calcium metabolism. It has a low incidence rate, accounting for 4-5% of all thyroid cancers<sup>2,5,6</sup>. Its occurrence is usually sporadic (84%)5 or hereditary (16%), with the latter occurring within the context of familial MTC or multiple endocrine neoplasia type 2 (MEN 2), which is associated with different mutations of the RET-4 proto-oncogene<sup>7</sup>. Sometimes, this cancer can spread to the lymph nodes, the lungs, or the liver, even before a thyroid nodule is detected. This type of thyroid cancer is more difficult to discover and treat<sup>2</sup>.

This neoplasm is characterized by secreting calcitonin, which is a useful marker for staging, residual disease detection, and long-term patient follow-up. It is a relative aggressive neoplasm since, despite its slow progression, 60-80% of cases have lymph node metastases at diagnosis<sup>8-12</sup>, which hinders fully curative therapy since more than 50% of patients have been observed to maintain calcitonin elevated levels after the first surgery<sup>2</sup>. Patients with the hereditary form tend to be younger and to have forms of the disease with more aggressive evolution, with cancer often being multifocal and bilateral<sup>2</sup>.

There are two types of thyroid cancer:

- Sporadic MTC accounts for approximately eight out of every 10 MTC cases, and is not hereditary. This cancer occurs mainly in older adults and it affects only one thyroid lobe<sup>2</sup>.
- Familial MTC is hereditary, and it can occur to 20-25% of members of each generation of a family. These cancers often develop during childhood or early adulthood and can spread early. Patients usually have cancer at several areas of both lobes. Familial MTC is often associated with an increased risk for other types of tumors<sup>2</sup>. Familial medullary thyroid cancer can be associated with hypercalcemia and adrenal tumors (pheochromocytomas)<sup>13</sup>.

Familial MTC is part of type 2 MEN, the classification of which is the following  $^{\rm 14,15}$ :

- MEN 2A (Sipple's syndrome): MTC, pheochromocytoma and primary hyperparathyroidism.
- MEN 2B: MTC, pheochromocytoma, intestinal and mucosal ganglioneuromatosis and marfanoid habitus<sup>14,15</sup>.

- Familial medullary thyroid carcinoma (FMTC): families with more than 10 mutation carriers, or families with multiple carriers or older than 50 years affected members, after detailed history-taking to rule out other endocrine tumors. Also, according to Eng, et al.<sup>16</sup> classification, families with four or more effected members.
- MEN 2A with lichen amyloidosis.
- MEN 2A or FMTC with Hirschsprung's disease<sup>4,14,15</sup>.

#### **CLINICAL PRESENTATION**

Usually, it appears in the form of a palpable thyroid nodule. It can be accompanied by systemic symptoms such as diarrhea and hot flashes, which are more common in patients with large tumors. Metastases to paratracheal and lateral cervical lymph nodes occur early in 20-30% of tumors < 1 cm, in 50% of tumors between 1 and 4 cm, and in up to 90% of tumors > 4 cm or T4. Rapidly growing tumors can occur with local invasion symptoms (dysphonia, dysphagia and dyspnea) in 15% of cases<sup>3</sup>.

Between 5 and 10% of cases present with distant metastasis to the lung, liver, bone and, less frequently, to the skin and central nervous system. Distant metastases are the main cause of death, and in half the cases they are already present at diagnosis. Lung metastases are macro- or micronodular, generally diffuse and bilateral. Bone metastases are osteolytic or osteoblastic lesions, with increased uptake on scintigram. Liver metastases appear as hyperechogenic images on echography; if they are small, they can be mistaken for liver hemangiomas<sup>3</sup>.

#### DIAGNOSIS

Genetic tests should be applied to all individuals diagnosed with medullary thyroid cancer. Genetic testing is considered the standard of care, not a research test. If it has been established that the patient has medullary thyroid cancer, the members of his/her immediate family should be examined to determine if there are genetic factors able to predict the development of MTC. Tests are focused on the RET proto-oncogene. In individuals with these genetic alterations, including children and infants, surgical removal of the thyroid gland before cancer has the chance to develop is highly likely to be a preventive cure. Nearly 100% of patients with the mutation (an abnormal sequence in the RET proto-oncogene) will eventually develop MTC. This specific mutation is useful to determine if the thyroid gland must be extirpated or not<sup>13</sup>.

The RET (REarranged during Transfection) proto-oncogene is found in chromosome 10q11.2, and it contains 12 exons. It encodes for a membrane receptor with tyrosine kinase activity. It is expressed in neural crest-derived cells: C cells, parathyroid cells, chromaffin cells of the adrenal medulla, enteric autonomic plexus and genitourinary tract<sup>3</sup>.

Medullary thyroid cancers normally produce calcitonin and carcinoembryonic antigen (CEA), which can be measured with blood tests<sup>13</sup>. Calcitonin (CT) is a 32-amino acid peptide, which is encoded in chromosome 11. It is the main tumor marker in MTC, and it shows high sensitivity and specificity. It is used for initial screening and postoperative follow-up<sup>3</sup>. Its levels are also increased in neonates, at pregnancy and breastfeeding, in kidney failure, thyroiditis, follicular tumors, C-cell hyperplasia (CCH) and in pancreas and respiratory tract endocrine tumors<sup>3</sup>. With lower sensitivity and specificity than calcitonin, the carcinoembryonic antigen (CEA) is useful for follow-up<sup>3</sup>.

Medullary thyroid cancer is unable to absorb iodine; therefore, radioactive iodine (RAI) should not be used in the treatment of MTC<sup>13</sup>. Several studies have demonstrated that MTC shows a high rate of locoregional involvement at diagnosis<sup>9,11</sup>, which is one of the main problems faced by these patients, since it allows for persistent disease and/or relapse to develop<sup>2</sup>.

#### TREATMENT

Surgery is the first line of treatment.

Primary treatment: total thyroidectomy and resection of all neoplastic tissue present in the neck. It is practiced in<sup>3</sup>:

- Patients with no clinical/imaging evidence of lymph node metastases: central compartment prophylactic resection (level VI)<sup>3</sup>.
- Suspected metastases limited to the central compartment: level VI resection; some endorse prophylactic lateral dissection<sup>3</sup>.
- Central and lateral involvement by pre-surgical imaging: central and lateral compartment resection (levels IIA, III, IV and V)<sup>3</sup>.
- In case of distant metastasis or locally advanced disease, a less aggressive surgery can be performed in order to preserve swallowing, speech, and parathyroid function<sup>3</sup>.

# TREATMENT OF HEREDITARY MEDULLARY THYROID CANCER

In the presence of pheochromocytoma: first, adrenal surgery. Identify the four parathyroid glands (staining with methylene blue). If they are normal-looking, they can be left or be implanted in a muscle<sup>3</sup>.

In the presence of hyperparathyroidism:

- If there is evidence of adenoma, it is dissected and the remaining ones are transplanted.
- If diffuse hyperplasia is observed, resection of 3½ glands and autologous transplantation of the remnant to the non-dominant forearm<sup>3</sup>.

Long-term prognosis is not as positive as in well-differentiated thyroid cancers. However, clinical trials have been carried out in recent years where new promising drugs have been tested for the treatment of progressive medullary thyroid cancer. One of these drugs is vandetanib (Caprelsa®), which has been approved by the US Food and Drug Administration (FDA) for selected patients with medullary thyroid cancer<sup>13</sup>.

#### MEDULLARY THYROID CARCINOMA METASTASIS TO THE ORAL CAVITY

Oral cancer accounts for approximately 8% of all malignant tumors, out of which 99% are carcinomas, with the most

common being tongue (27%), gum (17%), salivary glands (16%), and mouth floor (13%) carcinomas; the remaining 27% correspond to other sites. The male gender is most affected at a 2:1 ratio. It occurs almost invariably in patients older than 40 years. Metastases affecting the oral cavity account for 1% of malignant tumor lesions, and in 30% it is the first manifestation of a malignant tumor that has remained occult and asymptomatic. Clinically, they appear to be benign or reactive lesions of the oral cavity<sup>16-19</sup>. The bony component is more affected with regard to soft tissues, especially the mandible at the level of premolars and molars, probably because this is a highly vascularized area and because it contains hematopoietic tissue with higher activity<sup>20,21</sup>.

It is important to mention that nearly 50% of the medullary cancers have lymph node metastases at diagnosis and that 17.5% also have distant metastases<sup>22</sup>. Metastases to the oral cavity must be locally treated to avoid an ulcerated and painful lesion, to facilitate mastication, and to prevent local deformation. Treatment will be individual in each particular case, bearing in mind that if these lesions are removed by surgical treatment alone, the likelihood of relapse is high.

#### CASE PRESENTATION

This is the case of a 48-year-old female patient who worked as a janitor. She denied chronic-degenerative conditions as well as previous history of allergy, trauma, or surgical procedures. She was assessed at the oncology and maxillofacial surgery departments where she attended due to a three-month history of an oral region mass enlargement with bleeding, which caused discomfort and bleeding during mastication, as well as a one-year history of a mass in the neck with left predominance and progressive growth. The patient referred dyspnea and occasional pain, dysphagia for solids, and adynamia. The following was detected on physical examination: in the oral cavity, a friable, ulcerated lesion, bleeding on palpation, with granulomatous appearance, of approximately 6 x 6 cm in size was observed in the retromolar trigone, compromising the mobility of left superior first and second molars (Fig. 1); neck with multiple 1.5 cm



Figure 1. Oral cavity, where a right maxilla 3  $\times$  4-cm pediculated-looking tumor is observed.



Figure 2. Neck CT scan, axial section. Left lobe-dependent heterogeneous nodule, measuring  $8.6 \times 6.1 \times 6.1$  cm on its longest axes.

level IIA and IIIA adenopathies on the left side, as well as a bilateral neck tumor with left predominance, of  $15 \times 4 \text{ cm}$ , firm consistency, partially fixed on the left side, with right side tumor, of  $6 \times 4 \text{ cm}$  in size, hard consistency, partially fixed. A biopsy of the right maxilla tumor on August 28, 2015 reported maxillary region squamous cell cancer.

A surgical preparation protocol was started for the performance of the oral cavity tumor resection, as well as for neck tumorectomy. The chest radiograph did not show metastatic-appearing lesions. Facial skeleton and neck CT angiography reported a hypodense lesion in the single phase at the level of the right maxilla, which caused bone and pterygoid apophysis base erosion, measured approximately  $4.0 \times 3.7 \times 10^{-10}$ 3.2 cm on its largest axes, and showed enhancement after contrast medium IV administration; thyroid gland dimensions augmentation driven by a left lobe-dependent heterogeneous nodule that showed enhancement on the periphery, measured 8.6 x 6.1 x 6.1 cm on its largest axes, and caused the airway to shift to the right (Figs. 2 and 3). Thyroid profile: TSH: 2.71 mIU/l, total T3 (tri-iodothyronine): 1.59 ng/ml, free T3: 3.38 pg/ml, total T4 (thyroxin): 6.56 µg/dl, free T4: 0.78 ng/dl, parathyroid hormone: 25.2 pg/ml.

The patient underwent excisional biopsy with right maxillary region involved tooth (Fig. 4), as well as left hemithyroidectomy with the following results: left thyroid tumor, highly vascularized, with infiltration to adjacent tissues, of  $10 \times 6 \times 5$  cm in dimension (Fig. 5) and soft consistency; right thyroid was normal. The dissected hemithyroid specimen transoperative study reported follicular tumor vs. thyroid adenoma. Right hemithyroid and left inferior parathyroid gland were then resected, with recurrent laryngeal nerves being respected (Fig. 6). The surgical procedure concluded with no incidents or complications; bleeding: 300 ml. The patient had an adequate postoperative clinical evolution, with slight dysphonia, tolerance to the oral route, neck



Figure 3. Neck CT scan, coronal section. Tumor that is enhanced at the periphery and causes for airway to shift to the right.

drainage with scarce serohematic output, and discharge to her domicile was therefore decided.

Subsequently, the definitive anatomopathological diagnosis was established, with the following report: left thyroid lobe with medullary thyroid carcinoma; size: 6.7 x 5.2 x 4.9 cm, surgical margins negative for neoplastic cells, with data of vascular and perineural invasion, without extra-thyroidal extension. Right thyroid lobe free of medullary carcinoma, with data consistent with classic papillary micro-carcinoma, of size 0.5 cm, negative surgical margins, without vascular, perineural or extra-thyroidal invasion. The right maxillary lesion biopsy report indicated metastatic medullary carcinoma.

This diagnosis prompted the performance of a type III modified radical bilateral neck dissection, with the following findings being observed: 1 cm bilateral adenopathies on both sides of the neck, level III. The histopathology report referred: left-side neck lymphadenectomy with 15 lymph nodes without evidence of malignancy; left-side neck lymphadenectomy with nine malignancy free, inactive lymph nodes. A malignancy free parathyroid gland was identified. With these results, staging was: left medullary thyroid cancer, clinical stage IV (T3, N0, M1) and right micropapillary thyroid cancer, clinical stage I (T1a, N0, M0).

She was then assessed by the radio-oncology department, and the decision was made to administer adjuvant conformal radiotherapy to the neck with surgical bed area and oral cavity included, as well as jugular chains, at a dose of 68 Gy to the primary site in 34 fractions, which was completed without complications.

The patient is currently on treatment with levothyroxine 100 mcg/day, with slight dysphonia and tolerance to the oral route. On physical examination, no data consistent with clinical or radiological tumor recurrence were observed three months after treatment conclusion.



Figure 4. This image shows the oral cavity after excisional biopsy of the lesion.



Figure 5. Highly vascularized left thyroid tumor, with infiltration to adjacent tissues, of size 10 x 6 x 5 cm.



Figure 6. Thyroid bed, where thyroid gland complete resection is observed, since right hemithyroid and left inferior parathyroid gland were also dissected, with recurrent laryngeal nerves being respected.

#### DISCUSSION

Medullary thyroid cancer is a low-frequency and locally aggressive evolution malignancy, with an intermediate prognosis between differentiated and anaplastic cancers. However, these patients have been observed to achieve elevated long-term survival rates of 50-85% at 15 years of follow-up. Hence, we can envisage that adequately treating patients with hereditary MTC constitutes a huge challenge, especially within the context of MEN.

Available treatment approaches include the following. Surgery is regarded as the only curative treatment. In patients with residual or recurrent disease or distant metastasis, external beam radiation therapy (adjuvant or palliative) can be indicated in selected cases. There is also systemic chemotherapy, but it has very limited efficacy, with partial response only in 10-20% of cases (dacarbazine, 5-fluorouracil and doxorubicin). The presence of *RET* gene-activating mutations make it an alternative for future treatments targeting its inhibition and, therefore, this approach represents a possibility to improve progression-free survival of these patients<sup>3</sup>.

CT and CEA doubling time (DT) is significantly correlated with disease progression and is an important predictive factor for survival. In those patients with baseline detectable CT and no evidence of disease, CT and CEA should be determined at baseline and every six months to estimate DT. Based on the above, the following was concluded<sup>3</sup>:

- When CT DT was < 6 months, 5- and 10-year survival rate was 25 and 8%, respectively<sup>3</sup>;
- If CT DT was between 6-24 months, 5- and 10-year survival was 92 and 37%, in that order<sup>3</sup>;
- In patients with CT DT > 2 years, five-year survival was 100%<sup>3</sup>.

With regard to prognosis, 90% of patients with hereditary medullary thyroid cancer detected early by screening remain disease-free. According to the TNM classification, the 10-year survival rate for stages I, II, III and IV is 100, 93, 71, and 21%, respectively. Conversely, survival with distant metastasis is estimated to be 51% at one year, 26% at five years and 10% at 10 years. Poor prognostic factors include disease stage and old age at diagnosis. In multivariate analysis models, only stage and patient age at initial treatment are significant and independent indicators of survival<sup>3</sup>.

#### CONCLUSION

Metastatic medullary thyroid cancer has poor responses to radiotherapy and chemotherapy, and adequate screening and the possibility of early surgery are therefore essential in individuals at risk. In this regard, plasma calcitonin measurement in all patients with nodular thyroid disease could be proposed. It is important for genetic studies to be performed in all MTC cases in order to rule out associated pathologies. The only curative treatment in MTC is early and complete surgery, which requires an early diagnosis, with an option also being the implementation of an aggressive surgical approach, since medullary thyroid cancer is associated with an elevated rate of persisting disease and relapse. We should not forget that there are new investigational drugs based on molecular oncology as potential treatment for patients with medullary thyroid cancer at advanced stages.

#### **DECLARATION OF INTEREST**

The authors declare not having any conflicts of interests. The authors did not receive any kind of funding for the preparation of this article.

#### REFERENCES

- Guía de Práctica Clínica. Diagnóstico y Tratamiento del Nódulo Tiroideo. Evidencias y recomendaciones. Consejo de Salubridad General. CENETEC. México, Secretaria de Salud. 2009.
- Lanzarini SE, Marambio GA, Rodríguez MF, et al. Carcinoma Medular de Tiroides: Experiencia de 20 años. Rev. Chilena de Cirugía. 2010;62:15-21.
- Longobardi V. Guía de Práctica Clínica. Carcinoma Medular de Tiroides. Año 2011. Pp 1-12.
- Forga Llenas L. Genética del carcinoma medular de tiroides. Endocrinol Nutr. 2007;54:371-81.
- Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A National Cancer Data Base Report on 53,856 cases of Thyroid Carcinoma Treated in the U.S. 1985-1995. Cancer. 1998;83:2638-48.
- Wells SA, Franz C. Medullary carcinoma of the thyroid gland. World J Surg. 2000;24:952-6.
- Bugalho MJ, Domingues R, Rosa Santos J, Catarino AL, Sobrinho L. Mutation analysis of the RET protooncogen and early thyroidectomy: results of a Portuguese cancer centre. Surgery. 2007;141:90-5.
- Dottorini ME, Assi A, Sironi M, Sangalli G, Spreafico G, Colombo L. Multivariate analysis of patients with medullary thyroid carcinoma. Prognostic significance and impact on treatment of clinical and pathologic variables. Cancer. 1996;77:1556-65.
- Moley JF, DeBenedetti MK. Patterns of nodal metastases in palpable medullary thyroid carcinoma. Recommendations for extent of node dissection. Ann Surg. 1999;229:880-8.

- Scollo C, Baudin E, Travagli JP, et al. Rationale for central and bilateral lymph node dissection in sporadic and hereditary medullary thyroid cancer. J Clin Endocrinol Metab. 2003;88:2070-5.
- 11. Fleming JB, Lee JE, Bouvet M, et al. Surgical strategy for the treatment of medullary thyroid carcinoma. Ann Surg. 1999;230:697-707.
- Moley JF, DeBenedetti MK, Dilley WG, Tisell LE, Wells SA. Surgical management of patients with persistent or recurrent medullary thyroid cancer. J Intern Med. 1998;243:521-6.
- Guía Básica del Cáncer Tiroideo. ThyCa: Thyroid Cancer Survivor's Association Inc. 2013. Pp 8,9. Available at: www.thyca.org
- Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001;86:5658-71.
- Eng C, Clayton D, Schuffenecker I, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. International RET Mutation Consortium Analysis.
- Yu LS, Chen L. Mandible metastasis as the initial manifestation of breast carcinoma -report of a case. Chin Dent J. 1991;1098-103.
- JAMA. 1996; 276:1575-9. Shamin A, Bhargava Khan N, Ahmad Z, Afrez N. Metastatic mandibular adenocarcinoma. J IACM. 2007;8:196-8.
- Alvarez AC, Iglesias RB, Pazo IS, Delgado SG. Colon adenocarcinoma with metastasis to the gingiva. Med Oral Patol Oral Cir Bucal. 2006;11:E85-7.
- Sanchez JJ, Acebal BF, Arevalo ARE, Molina MM. Metastatic tumours in upper maxillary bone of esophageal Adenocarcinoma. A case report. Med Oral Patol Oral Cir Bucal. 2005;10:252-7.
- Anthony WT, Agargwal N, Joseph PG. Oral cavity metastasis of renal cell carcinoma: A case report. J Med Case Reports. 2008;2:313.
- Halachmi S. Madeb R, Madjar S, Wald M, River Y, Nativ O. Numb chin syndrome as the presenting symptom of metastatic prostate carcinoma. Urology. 2000;55:286.
- Medrano OZME, Rodriguez-Cuevas SA, Labastida AS, Gomez AF. Cáncer medular de tiroides. Oncología (Rev Mex Oncol) 1992;7:20-3.


## CLINICAL CASE

SOCIEDAD MEXICANA DE ONCOLOGÍA, A.C. GACETA MEXICANA DE ONCOLOGÍA WWW.gamo-smeo.com



# Treatment with Radium 223 in a Patient with Castration-Resistant Metastatic Prostate Cancer: A Case Report

## Christian Patricio Camacho-Limas\*, Alberto Villalobos-Prieto and Raquel Gerson-Cwilich

Department of Medical Oncology, American-British Cowdray Medical Center, Mexico City, Mexico

Received for publication: 30 June 2016; accepted for publication: 25 February 2017 Available online: 10 July 2017

**KEYWORDS** 

Prostate cancer; Castration-resistant; Radium 223 Abstract Introduction: Prostate cancer is the second cause of cancer-related death. The treatment for metastatic disease with bone activity is multimodal and includes external beam radiation therapy and radiopharmaceuticals with bone affinity. The therapeutic decision is based on the presence or absence of symptoms, on prostate-specific antigen behavior, and on the distribution of metastatic disease, where the role of chemotherapy is well defined (presence or absence of visceral metastases or only bone disease). Radium-223 dichloride (223-Ra) is a calcium-mimetic radiopharmaceutical with activity in osteoblastic lesions that has demonstrated an increase in the time to first skeletal symptomatic event, a decrease in alkaline phosphatase and increased quality of life, with good tolerance. Case presentation: An 83-year old male diagnosed in 2011 with prostate adenocarcinoma with bone metastases, treated with hormone blockade for two years. In 2013, he developed hormone-refractory disease progression at the bone level, which was treated with abiraterone in 2014, with prostate-specific antigen elevation and bone pain due to bone progression without visceral disease. In January 2015, radium-223 was indicated every 28 days for four cycles, with important symptom improvement and adequate toxicity profile. Conclusions: Treatment with radium-223 provides adequate pain control with an important decrease of alkaline phosphatase and quality of life improvement, offering yet another alternative for patients with castration-resistant metastatic prostate cancer and symptomatic bone disease, with an acceptable toxicity profile. (creativecommons.org/licenses/by-nc-nd/4.0/).

\*E-mail for correspondence: dr.camacholimas@gmail.com (C.P. Camacho-Limas)

http://dx.doi.org/10.24875/j.gamo.17000012

1665-9201 / © 2017 Sociedad Mexicana de Oncología. Publicado por Permanyer México. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

## INTRODUCTION

Prostate cancer is the most common non-cutaneous malignant tumor in men in the USA, it is the second cause of cancer-related death, and it is acknowledged as the most common malignancy in males older than 50 years. Average life expectancy for Mexican males in the year 2008 was 75 years, which increases the incidence and mortality of this malignancy.

In spite of these figures, most cases are diagnosed at early stages where the likelihood of cure is high, with only 5% of patients being estimated to present with advanced phases at diagnosis.

Up to 20-30% of patients diagnosed with local disease will have recurrence in the systemic form.

In patients with metastatic prostate cancer, the predominant site of disease is the bone. Bone metastases are a common event (65-85%), and have a notorious clinical impact by generating symptoms such as pain, weakness, or functional impairment.

Established treatment for advanced prostatic cancer initially includes androgen-blockage therapy. This approach shows high efficacy, which is estimated at 80%. However, benefit duration is limited in time, with a median of 18-24 months and with most patients progressing to a castration-resistance situation.

In this context, there are therapeutic options such as treatments that interfere with tumor-growth androgenic stimulus (abiraterone, enzalutamide), immunotherapy and chemotherapy with taxanes, among others. If patients show multifocal osteoblastic bone metastases, systemic treatments or external beam radiation therapy is administered and, if uncontrollable, therapeutic radiopharmaceuticals with bone affinity may offer significant palliative benefit.

Thus, the therapeutic decision is dependent on the presence or absence of symptoms, on prostate-specific antigen (PSA) doubling time, and on the distribution of metastatic disease (presence or absence of visceral metastases or only bone disease).

#### RADIUM-223 DICHLORIDE (223-RA)

Radium-223 dichloride (223-Ra) has been approved for the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases and without known visceral metastases.

Radium-223 dichloride (223-Ra) is a radiopharmaceutical for alpha particle-emission treatment that mimics calcium and selectively binds to the bone, specifically to areas of bone metastasis where it forms complexes with bone hydroxyapatite. Alpha particles' linear transference elevated energy (80 keV/micrometer) causes double-stranded DNA breaks in adjacent tumor cells rather frequently, which result in a potent cytotoxic effect.

It also elicits additional effects in the tumor microenvironment, including osteoblasts and osteoclasts; radium (223-Ra) alpha particles travel less than 100 micrometers (less than 10 cell diameters), which minimizes damage to normal surrounding tissue.

### EFFICACY

Radium-223 dichloride (223-Ra) efficacy has been assessed in 921 patients in a phase III clinical trial (BC1-06, 15245 or ALSYMPCA) and in 286 patients included in three phase II clinical trials (BC1-02, BC1-03, BC1-04). Patients had to be diagnosed with castration-resistant prostate cancer with bone metastases.

The ALSYMPCA study was a multi-center, randomized, double-blind trial where radium-223 dichloride (223-Ra) and the best standard of care was compared with placebo and the best standard of care, with best standard of care being defined as local external beam radiation therapy or treatment with bisphosphonates, corticosteroids, anti-androgens, estrogens, estramustine or ketoconazole. The study demonstrated that the treatment with radium-223 prolonged the time to a first symptomatic skeletal event, reduced alkaline phosphatase, improved quality of life, and was well tolerated. A PSA decrease was observed in a minority of patients.

## SAFETY

Safety data are essentially based on 600 patients of the AL-SYMPCA trial who had to be treated with a total of six intravenous injections of 50 kBq/kg of radium-223 dichloride (223-Ra) at four-week intervals between administrations.

In this study, treatment mean duration was 141 days for the radium-223 dichloride (223-Ra) group and 128 days for the placebo group patients, with a mean number of doses of 5.1 and 4.5, respectively.

The most common adverse reactions reported with radium-223 dichloride (223-Ra) include nausea (36%), diarrhea (25%), vomiting (19%), thrombocytopenia (12%), neutropenia (5%), and leukopenia (4%).

### CASE PRESENTATION

This is the case of an 83-year-old male patient with a history of prostate adenocarcinoma with bone metastasis (lumbar) diagnosed in 2011. He was treated with hormone blockade for two years, and experienced progression of the disease at the bone level in 2013, demonstrated by scintigraphy (hip, lumbar spine, and shoulder), which was defined as castration-resistant prostate cancer. The patient was therefore initiated on abiraterone therapy in 2014 but showed progressive elevation of the tumor marker (PSA) and bone progression, as well as bone pain without visceral disease. In view of this, treatment with radium-223 dichloride (223-Ra) was indicated in January 2015. The patient received four administrations, with an important improvement in symptoms such as bone pain and alkaline phosphatase and PSA levels, with no data consistent with hematologic toxicity being found.

### DISCUSSION

Radium-223 dichloride (223-Ra) is indicated for the treatment of male adult patients with castration-resistant pros-



Figure 1. Evolution by imaging in the course of the treatment with radium-223 dichloride (223-Ra).



Figure 2. Alkaline phosphatase.

tate cancer, symptomatic bone metastases, and without known visceral metastases. Therefore, this indication suggests that it can be administered both in patients with no previous treatment with chemotherapy and in patients who have failed to respond to first-line chemotherapy.

There are a total of seven clinical trials available to support radium-223 dichloride (223-Ra) efficacy and safety (including pharmacokinetics), although no study so far has been positive for overall survival. However, there are sufficient data to support that the administration of this treatment helps to improve symptoms associated with symptomatic metastatic bone disease such as pain, with an adequate toxicity profile at the hematologic level, as in the present case. There was no PSA-associated therapeutic response, but an important symptom improvement was maintained. Median treatment duration was 118 days, with an important decrease in alkaline phosphatase and adequate



Figure 3. Hemoglobin.



Figure 4. Leukocytes and neutrophils.



Figure 5. Platelets.

pain control, and even with a decrease in opioid medication support, most of which are clearly dose-limiting and sometimes can elicit undesirable effects that further deteriorate patient quality of life.

## CONCLUSION

Treatment with radium-223 dichloride (223-Ra) is yet another alternative for patients diagnosed with castration-resistant metastatic prostate cancer with bone tumor activity and associated pain. Radium-223 dichloride (223-Ra) therapy offers an acceptable toxicity profile, with an impact on our patient's quality of life.



Figure 6. Prostate-specific antigen.

#### REFERENCES

- Gónzalez del Alba A. Cáncer de prostate. Available at: http://www. seom.org/en/informacion-sobre-el-cancer/info-tiposcancer/genitourinario/prostata.
- Incidencia del cáncer de próstata. Available at: https://www.aecc.es/ SobreElCancer/CancerPorLocalizacion/cancerdeprostata/Paginas/incidencia.aspx.
- Ferlay J, Soerjomataram I, GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC.) Int J Cancer. 2013;132:1133-45.
- Duran I, Garzón C, Sánchez A, et al. Cost analysis of skeletal-related events in Spanish patients with bone metastases from solid tumours. Clin Transl Oncol. 2014;16:322-9.
- 5. Xofigo SPC. Available at: http://www.ema.europa.eu/docs.
- Assessment report for Xofigo (radium chloride (223Ra). Available at: http://www.ema.europa.eu/docs/en\_GB/document\_library/EPAR Public\_assessment\_report/human/002653/WC500156174.pdf
- Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213-23.
- Current use and future needs of radiopharmaceuticals labeled with radionuclides produced in reactors and possible alternatives.
- Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012;13:983-92.
- Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367:1187-97.
- Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363:411-22.
- Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. J Clin Oncol. 2008;26:242-5.
- de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376:1147-54.
- Stabin MG. Dosimetric and radiobiologial considerations. In: Ell PJ, Gambhir SS. Nuclear Medicine in clinical diagnosis and treatment. Third Edition. Churchill Livingstone 2004; pp. 363-73.



## CLINICAL CASE

# SOCIEDAD MEXICANA DE ONCOLOGÍA, A.C. GACETA MEXICANA DE ONCOLOGÍA WWW.gamo-smeo.com



# Incidentally-Diagnosed Multiple Endocrine Neoplasia IIA (Sipple Syndrome) with Bilateral Pheochromocytoma and Medullary Thyroid Carcinoma

Vera Eunice Robles-Pérez<sup>1,\*</sup>, Jeannette Liliana Córdova-López<sup>2</sup>, Carlos Alejandro Hernández-González<sup>3</sup>, Jorge Alberto Medina-Medina<sup>4</sup>, Víctor Hugo Ramos-Cano<sup>5</sup> and Eurídice Robles-Pérez<sup>6</sup>

<sup>1</sup>Department of Surgical Oncology, Hospital Regional 1° de Octubre, ISSSTE; <sup>2</sup>Department of Pediatric Cardiology, Hospital Pediatrico de Azcapotzalco, SS CDMX; <sup>3</sup>Department of Pathology and <sup>4</sup>Department of General Surgery, Hospital Regional 1° de Octubre, ISSSTE; <sup>5</sup>Department of Cardiovascular Surgery and <sup>6</sup>Department of Thoracic Surgery, Hospital Juárez de México, SS; Mexico City, Mexico

Received for publication: 7 January 2017; accepted for publication: 25 February 2017 Available online: 10 July 2017

## **KEYWORDS**

Multiple endocrine neoplasia IIA; Medullary thyroid carcinoma; Pheochromocytoma; RET proto-oncogene **Abstract** Multiple endocrine neoplasia IIA, also known as Sipple syndrome, is a rare entity that is difficult to diagnose and potentially fatal and is caused by RET proto-oncogene mutations. The importance of its diagnosis and determination of this mutation in the patient and his/her consanguineous relatives lies in avoiding the appearance of medullary thyroid cancer by means of prophylactic thyroidectomy and follow-up at the appearance of pheochromocytoma or parathyroid adenoma. We present the case of a female asymptomatic patient with the TGC34AGC-Cys634Arg mutation who was diagnosed with medullary thyroid carcinoma and bilateral pheochromocytoma, had a family history of thyroid and adrenal tumor-related deaths, was treated for curative purposes, and in whom the diagnosis was suspected by screening studies. (creativecommons.org/licenses/by-nc-nd/4.0/).

\*E-mail for correspondence: roblesvera@yahoo.com (V.E. Robles-Pérez)

http://dx.doi.org/10.24875/j.gamo.17000013

1665-9201 / © 2017 Sociedad Mexicana de Oncología. Publicado por Permanyer México. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (http://creativecommons.org/licenses/by-nc-nd/4.0/).

## INTRODUCTION

Sipple syndrome, an eponym used to designate multiple endocrine neoplasia type IIA (OMIM #171400)<sup>1</sup>, is a rare and potentially fatal disease that affects one in every 40,000 people. It is an autosomal recessive condition, the clinical spectrum of which includes the presence of pheochromocytoma, medullary thyroid carcinoma, and parathyroid adenomas<sup>2</sup>.

The description of this disease dates back to 1961 when Dr. John H. Sipple presented a series of 537 cases of pheochromocytoma, out of which five were strongly associated with thyroid gland carcinoma<sup>3</sup>. Subsequently, in 1965, Schimke demonstrated the association of pheochromocytoma with medullary thyroid carcinoma<sup>4</sup>. Finally, both these conditions and the presence of parathyroid adenomas have distinguished this entity.

Clinical diagnosis is rarely suspected and it occurs mostly during study protocols of patients who may display: (i) high blood pressure secondary to a pheochromocytoma, (ii) hypercalcemia in the causative study of pyeloureteral lithiasis, or (iii) during the screening of a thyroid nodule that results in medullary cancer when there is a family history of this type of neoplasm. However, many times the syndrome goes unnoticed and the patient dies without a diagnosis, which puts the family integrity at risk since transmission of the disease occurs in up to 50% of the offspring. If, on the other hand, we consider that the diagnosis of this syndrome forces to consider prophylactic thyroidectomy at ages as early as five years, given that these patients will develop medullary thyroid cancer in up to 95% of cases, we can consider Sipple syndrome to be a highly important entity.

Since 1998, the RET proto-oncogene has been associated with medullary thyroid carcinoma as a result of studies carried out by Shirahama, et al.<sup>5</sup>. In 2000, the molecular mechanisms likely involved in the development of tumors by mutations in this proto-oncogene were discovered by Huang, et al.<sup>6</sup> and Koch, et al.<sup>7</sup>. Currently, the cause of Sipple syndrome is accepted to be a mutation in the RET proto-oncogene, which encodes for a tyrosine kinase receptor located in chromosome 10q11.21. There are 52 documented allelic variants<sup>8</sup>, with 17 of them being involved with the development of Sipple syndrome. From 73-85% are found at codon 634 in exon 11 (C634R and C634Y) and 10-20% at codons 609, 611, 618, and 620 in exon 10.

Molecular diagnosis of this syndrome can be carried out by demonstrating RET gene mutations, which is the gold standard; however, the diagnosis can also be established with the demonstration of two neoplasias in a single individual or in a first-degree relative. If a genetic study is not feasible, this should not delay diagnosis and treatment<sup>9,10</sup>.

Wells, et al.<sup>11</sup> demonstrated that total thyroidectomy in asymptomatic patients with proto-oncogene RET mutations can prevent or cure medullary thyroid carcinoma, which is a neoplasm with multifocal, bilateral presentation that spreads early to the lymph nodes. Currently, there are protocols that justify this surgery in certain types of RET mutations<sup>12-14</sup>.

This syndrome is regularly accompanied by pheochromocytoma and parathyroid adenoma. Other characteristics that may be included are Hirschsprung's disease and Cushing syndrome<sup>15</sup>.

## **CLINICAL CASE**

This is the case of a 50-year-old female patient with a family history of thyroid tumors in her great-grandmother, grandfather, aunt, and mother, all of them by the maternal line (Figs. 1-6 and Table 1), who had lactate dehydrogenase and aspartate and alanine aminotransferase elevations in a routine yearly checkup, which prompted for a liver ultrasound to be performed where lesions were detected in the hepato- and splenorenal spaces. Liver triphasic CT scan showed tumors dependent on both adrenal glands. In addition, metanephrine plasma levels were elevated. Finally, a metaiodobenzylguanidine-1<sup>131</sup> uptake study was performed, which generated sufficient evidence to consider the bilateral pheochromocytoma diagnosis, with surgery being indicated.

Preoperatively, alpha-adrenergic receptor blockage was applied, followed by beta blockage for surgical extirpation by the laparoscopic route, which was carried out with no accidents or incidents and with right and left tumors being found of 3 and 5 cm at the longest diameter, respectively. The histopathological analysis result indicated bilateral pheochromocytoma.

Although the CT scan, the bone scintigraphy, and the metaiodobenzylguanidine-I<sup>131</sup> uptake study allowed for the presence of catecholamine-producing tissue other than that found in the adrenal glands to be ruled out, these tests, together with serum calcium and calcitonin elevated levels, allowed for a lesion in the thyroid gland right lobe to be detected; thyroid gland function tests were normal.

Following the protocol, a neck CT scan was performed where bilateral thyroid nodules and right-side neck adenomegalies were found, which warranted an ultrasound-guided fine-needle aspiration biopsy that turned out to be highly suspicious of malignancy.

Owing to these findings, the patient underwent total thyroidectomy and type III right-side neck and central compartment radical resection, with the surgery encompassing two parathyroid glands' excision. The histopathology result showed bilateral medullary thyroid carcinoma with metastasis to right-side lymph nodes and two parathyroid glands with no alterations. With these findings, the Sipple syndrome diagnosis was established and the case was referred to genetic counseling with the purpose to include the family in a protocol in order to determine the performance of prophylactic thyroidectomy.

The sequencing studies for the RET gene showed a thymine-adenine heterozygous mutation at the 634 position (TGC634AGC $\rightarrow$ Cys634Arg).

Currently, the patient is asymptomatic on thyroid-replacement therapy, steroid supplementation, and thyroid pathology management. Calcitonin levels are currently at 137 pg/ml, and genetic sequencing studies will be carried out in her consanguineous relatives.



Figure 1. Family tree showing the recurrence of pheochromocytoma and medullary thyroid cancer.

## DISCUSSION

Sipple syndrome or multiple endocrine neoplasia type IIA is a rare condition that commonly produces initial clinical signs and symptoms that mostly can be grouped into four types of presentation:

The first one corresponds to those symptoms resulting from blood-circulating catecholamine level increase owing to functioning tumors deriving from chromaffin cell proliferation. Patients initially experience headache, sweating, tachycardia, nervousness and irritability, weight loss, and sometimes abdominal or chest pain. Many of them are diag-



Figure 2. Magnetic resonance imaging revealing bilateral adrenal tumors.

Figure 3. Scintigraphy with metaiodobenzylguanidine- $\mathsf{I}^{131}$  showing bilateral adrenal region and thyroid uptake.



Figure 4. Neck CT-scan revealing heterogeneous, vascularized nodule on right thyroid lobe, as well as bilateral calcifications.

nosed with high blood pressure and cases are not rare where symptoms may be confused with panic attacks, generalized anxiety disorder, or other similar conditions that ultimately are later diagnosed as pheochromocytomas<sup>16</sup>, and in the case of this syndrome, sometimes when patients have already developed medullary thyroid cancer.

A second spectrum corresponds to asymptomatic patients who accidentally feel a cervical growth or palpate one or

several lymph nodes that grow in number and size over time and where a thyroid nodule is identified, which after the corresponding protocol is diagnosed as medullary thyroid cancer<sup>17</sup>.

The third type of manifestation corresponds to those patients with generalized joint pain, abdominal pain, depression, or urolithiasis, where the protocol reveals the presence of hypercalcemia, which drives to the suspicion of hyperparathyroidism and parathyroid adenoma<sup>18</sup>.

Finally, there is a type of patients in whom one or more of the main Sipple syndrome components indirectly develop manifestations that direct the diagnostic protocol towards other entities such as peptic ulcer<sup>19</sup>, cutaneous lichen amyloidosis<sup>20</sup>, Cushing syndrome<sup>21</sup>, and catecholamine-induced cardiomyopathy22; even thyroidectomy for causes other than medullary thyroid cancer has been reported to yield parafollicular cell hyperplasia as a result, which raises suspicion and subsequently leads to diagnosis<sup>23</sup>. There is even one case reported by Casey, et al.<sup>24</sup>, who decided to implement a diagnostic protocol in a 35-year-old female patient with fatigue and weight loss, and discovered hepatic masses that turned out to be medullary thyroid cancer metastases. which differentiates this case from ours where no distant metastasis was demonstrated. However, no entirely asymptomatic case has been vet reported in the literature.

The presence of bilateral pheochromocytoma and medullary thyroid cancer at diagnosis is infrequent, but it is necessary, by itself, for the type IIA multiple endocrine neoplasia diagnosis to be integrated, and this is the reason why the pheochromocytomas were excised and total thyroidectomy was practiced.

In the presence of a medullary thyroid cancer index case, familial genetic study is indispensable. Prophylactic thyroidectomy is the only curative treatment, with it being dependent on the mutation type<sup>25,26</sup>. Since the coincidence of presence of the disease and the mutation-carrier status is higher than 95%, the study has to be also performed in consanguineous relatives.



Figure 5. Left (A) and right (B) adrenalectomy.





Figure 6. Electrophoretogram showing thymine-adenine heterozygous mutation at the 634 position (TGC634AGC - Cys634Arg).

## CONCLUSION

Sipple syndrome is rare disease with different presentations. It is potentially lethal and its opportune diagnosis has consequences not only for the patient's life but also for that of his/her relatives since this is an autosomal-dominant familial syndrome.

In most cases, the diagnosis is based on suspicion or is established by the presence of pheochromocytoma, medullary thyroid carcinoma, and/or parathyroid adenoma, even more so if any of these conditions is recurrent in the family.

Even when it is the gold standard, the demonstration of a specific mutation in the RET proto-oncogene should not delay the diagnosis and treatment of the disease in patients in whom it cannot be carried out.

Declaration of interest

The authors declare not having any social, economic, ethical and/or moral conflict of interest with regard to the investigation, development, and presentation of this work.

## REFERENCES

- Omim.org. (2017). OMIM Entry # 171400 MULTIPLE ENDOCRINE NEO-PLASIA, TYPE IIA; MEN2A. Available at: http://omim.org/entry/171400 (Accessed 22 Jan. 2017).
- Marquard J, Eng C. Multiple Endocrine Neoplasia Type 2. 1999 Sep 27 [Updated 2015 Jun 25]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews<sup>®</sup> [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Available at: https://www.ncbi.nlm.nih.gov/ books/NBK1257/ (Accessed 22 Jan. 2017).
- Sipple J. The association of pheochromocytoma with carcinoma of the thyroid gland. Am J Med. 1961;31:163-6.
- Schimke, R. Familial amyloid-producing medullary thyroid carcinoma and pheochromocytoma. Ann Intern Med. 1965;63:1027-39.
- Shirahama S, Ogura K, Takami H, et al. Mutational analysis of the RET proto-oncogene in 71 Japanese patients with medullary thyroid carcinoma. J Hum Genet. 1998;43:101-6.
- 6. Huang SC, Koch CA, Vortmeyer AO, et al. Duplication of the mutant RET allele in trisomy 10 or loss of the wild-type allele in multiple endocrine neoplasia type 2-associated pheochromocytomas. Cancer Res. 2000;60:6223-6.
- Koch C, Huang SC, Moley JF, et al. Allelic imbalance of the mutant and wild-type RET allele in MEN 2A-associated medullary thyroid carcinoma. Oncogene. 2001;20:7809-11.
- Omim.org. (2017). OMIM RET Allelic Variants 164761. Available at: http://omim.org/allelicVariant/164761 (Accessed 22 Jan. 2017).
- Kloos RT, Eng C, Evans DB, et al. American Thyroid Association Guidelines Task Force. Medullary Thyroid Cancer: Management Guidelines of the American Thyroid Association. Thyroid. 2009;19:565-612.
- Moline J, Eng C. Multiple endocrine neoplasia type 2: An overview. Genet Med. 2011;13:755-64.
- Wells SA, Chi DD, Toshima K, et al. Predictive DNA testing and prophylactic thyroidectomy in patients at risk for multiple endocrine neoplasia type 2A. Ann Surg. 1994;220:237-50.
- Skinner M, Moley JA, Dilley WG, Owzar K, Debenedetti MK, Wells SA, et al. Prophylactic thyroidectomy in multiple endocrine neoplasia Type 2A. N Engl J Med. 2005;353:1105-13.
- 13. Fahey T. Prophylactic thyroidectomy in multiple endocrine neoplasia type 2A. Yearbook of Surgery. 2006;144.

	Baseline	Final (after surgeries)	Reference values
Alanine aminotransferase	234 IU/l	29 IU/l	10-40 IU/l
Aspartate aminotransferase	154 IU/l	23 IU/l	10-42 IU/l
Lactate dehydrogenase	259 IU/l	196 IU/l	0-248 IU/l
Urinary metanephrines			
Total metanephrines	1609.49 µg/24 h	204 µg/24 h	< 900 µg/24 h
Urinary metanephrines	638.60 µg/24 h	74 µg/24 h	< 350 µg/24 h
Normetanephrines	970.89 µg/24 h	130 µg/24 h	< 600 µg/24 h
Noradrenaline	109.2 µg/24 h	80 µg/24 h	0-90 µg/24 h
Adrenaline	27 µg/24 h	23 µg/24 h	0-20 µg/24 h
Dopamine	1,050.59 µg/24 h	115 µg/24 h	0-600 µg/24 h
Plasma metanephrines	93.46 pg/ml	40 pg/ml	< 90 pg/ml
Plasma free metanephrines	83.0 pg/ml	56 pg/ml	0-62 pg/ml
Plasma free normetanephrines	445 pg/ml	120 pg/ml	0-145 pg/ml
Calcitonin	4,010 pg/ml	137 pg/ml	0-11.5 pg/ml
Thyroid function tests			
TSH	1.68 µIU/ml	0.02 µIU/ml	0.30-4.67 µIU/ml
Total T3	0.96 ng/ml	0.86 ng/ml	0.76-2.2 ng/ml
Total T4	8.26 μg/dl	13.20 μg/dl	4.5-12.60 μg/dl
Free T4	1.30 ng/dl	2.51 ng/dl	0.71-1.85 ng/dl

Table 1. Baseline and end-of-treatment laboratory tests

h: hours; TSH: thyroid-stimulating hormone.

- Glynn RW, Cashman EC, Doody J, Phelan E, Russell JD, Timon C. et al. Prophylactic total thyroidectomy using the minimally invasive video-assisted approach in children with multiple endocrine neoplasia type 2. Head Neck. 2014;36:768-71.
- Opsahl EM, Brauckhoff M, Schlichting E, et al. A nationwide study of multiple endocrine neoplasia type 2A in Norway: predictive and prognostic factors for the clinical course of medullary thyroid carcinoma. Thyroid. 2016;26:1225-38.
- Tsang V, Tacon L, Learoyd D, Robinson B. Pheochromocytomas in multiple endocrine neoplasia Type 2. Recent Results Cancer Res. 2015;204:157-78.
- Morlán Herrador L, de Arriba A, Miguel G, Ferrera M, Labarta JI. [Study of medullary thyroid carcinoma from a proband]. Arch Argent Pediatr. 2016;114:e421-4.
- Alevizaki M. Saltiki K. Primary hyperparathyroidism in MEN2 syndromes. Recent Results Cancer Res. 2015;204:179-86.
- Weledji E. A rare presentation of multiple endocrine neoplasia (MEN) type 2A syndrome. Ann Med Surg. 2016;5:35-7.
- Birla S, Singla R, Sharma A, Tandon N. Rare manifestation of multiple endocrine neoplasia type 2A & cutaneous lichen amyloidosis in a family with RET gene mutation. Indian J Med Res. 2014;139:779-81.

- Borzouei S, Mousavi Bahar SH, Fereydouni MA, Salimbahrami SA, Taghipour M. Multiple endocrine neoplasia type IIa associated with Cushing's syndrome. Arch Iran Med. 2014;17:451-4.
- Gómez RM, Gonzáez VF, Sánchez AM. Sipple's syndrome presenting acutely as severe heart failure. Eur J Emerg Med. 2002;9:171-4.
- Sakorafas G, Nasikas D, Thanos D, Gantzoulas S. Incidental thyroid c cell hyperplasia: clinical significance and implications in practice. Oncol Res Treat. 2015;38:249-52.
- 24. Casey R, Bell M, Keane M, Smyth A. An unusual presentation of MEN2A. BMJ Case Rep. 2013;2013.
- Krampitz G, Norton J. RET gene mutations (genotype and phenotype) of multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma. Cancer. 2014;120:1920-31.
- Wells SA, Asa SL, Dralle H, et al. American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma. Thyroid. 2015;25:567-610.