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

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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 ipilimumab-treated 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/).

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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)1.

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 melanoma1.

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, red-haired, 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, bright blonde 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.

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.

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.

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. (Clinical Stage, Table 1).

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.

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Pathologic classification

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| T1b | N0 | M0 |
| T2a | NO | M0 |
| T2b | NO | M0 |
| T3a | NO | M0 |
| T3b | NO | M0 |
| T4a | NO | M0 |
| T4b | NO | M0 |
| T1-4a | N1a | M0 |
| T1-4b | N1a | M0 |
| T1-4b | N2a | M0 |
| T1-4b | N2b | M0 |
| T1-4a | N2c | M0 |
| T1-4b | N1b | M0 |
| T1-4b | N2b | M0 |
| T1-4b | N2c | M0 |
| Any T | N3 | M0 |
| IV | Any T | Any N | M1 |
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.

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 (≤ 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 cm, 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.

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-α2b, 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 high-dose administration, which involves an induction with intravenous interferon-α2b at a 20 MU/m² dose five days a week for four weeks, followed by maintenance treatment with subcutaneous interferon-α2b at a dose of 10 MU/m² 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.

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.

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.

**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.

**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.

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.

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).

**Tremelimumab**

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

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<th>Table 2. Summary of long-term results for ipilimumab in metastatic melanoma</th>
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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 (FcγR) 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)19,20.

**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-cells21.

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 dacarbazine22.

Another antagonist antibody to specifically compete with the interaction between PD-1 and PD-L1, 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 toxicities 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, non-small cell lung cancer, and renal cancer, which may result in additional indications for this immunotherapy23.

**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%.

**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%); CSII, four (30.8%); CSIV, three (23.1%); the detailed clinical status is shown in Table 4. Histological lineages, in
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: 8-24), with CNS involvement being 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) of patients who died during the follow-up period (Fig. 1).

Factors associated with patient response to the treatment with ipilimumab

Hispanic ethnicity was identified as a protective 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-
under 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 (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>
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<th>Table 6. Therapeutic response characteristics (n = 13)</th>
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<tr>
<td><strong>Response characteristics</strong></td>
</tr>
<tr>
<td>Overall survival</td>
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<tr>
<td>Progression-free survival</td>
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<tr>
<td>Complete response</td>
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<tr>
<td>Partial response</td>
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<tr>
<td>Stable disease</td>
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<td>Progressive disease</td>
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*Months, median (IQR).
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.

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