The burden of multiple myeloma in Mexico: an epidemiologic investigation of the national health system

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Abstract

Introduction: Although multiple myeloma (MM) represents only 1% of the global burden of cancer, its prevalence increases as the population ages. Monitoring our progress to treat MM requires novel tools for epidemiologic surveillance. **Methods:** We developed a surrogate measure for the burden of MM in Mexico during 2015, representing the number of prevalent and incident cases of MM at every public and private Mexican health institution. We identified individuals through the ICD-10 codes C90.0-C90.3. Hospitalizations and mortality due to MM were also studied. The number of cases was standardized to represent the age-specific Mexican population obtained through census data. We conducted structured interviews to clinicians to gather data on treatment and clinical characteristics. **Results:** In 2015, 2569 patients with MM were attended, 2039 unique patients were hospitalized, and 1169 patients died in the Mexican health system. The incidence rate for MM was $1.16 \times 100,000$ inhabitants-year during the study period. Therapies were consistent between the public and private sectors. Incidence was higher among elder men. **Conclusion:** Our findings align with epidemiologic trends in the developing world. As we face aging of the population and new therapies extend the survival of patients with MM, our surrogate will be useful for epidemiologic surveillance.

Key words: Multiple myeloma. Mexico. Burden. Epidemiology. Incidence rate.

La carga del mieloma múltiple en México: una investigación epidemiológica del Sistema Nacional de Salud

Resumen

Introducción: Aunque el mieloma múltiple (MM) representa el 1% de la carga del cáncer, su prevalencia aumenta conforme la población envejece. Se requieren herramientas novedosas de vigilancia epidemiológica para monitorizar nuestros avances en su tratamiento. **Métodos:** Desarrollamos una medida sustituta para la carga de MM en 2015, representando la prevalencia e incidencia del MM en México. Identificamos los casos mediante los códigos CIE-10 C90.0-C90.3. Estudiamos las hospitalizaciones y la mortalidad por MM. Se estandarizó el número de casos para representar a la población por grupos de edad, conforme a datos obtenidos de censos. Realizamos entrevistas a especialistas para obtener datos sobre el tratamiento y las características clínicas. **Resultados:** En 2015 en México se atendieron 2,569 pacientes con MM, se hospitalizaron 2,039, y fallecieron 1,169. La tasa de incidencia para MM fue de $1.16 \times 100,000$ habitantes en este año, siendo mayor en hombres de la tercera edad. El tratamiento fue similar en los sectores público y privado. **Conclusión:** Nuestros hallazgos coinciden con las tendencias epidemiológicas de países en desarrollo. Nuestra medida servirá para la vigilancia epidemiológica ante la realidad de una población de edad cada vez mayor y el uso de terapias que prolongan la supervivencia de los pacientes con MM.

Palabras clave: Mieloma múltiple. Carga. Epidemiología. Tasa de incidencia.

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Introduction

Despite the fact that multiple myeloma (MM) represents only 1% of total cancer burden, it ranks second in the world in the prevalence of hematologic neoplasms¹. Since MM mainly affects individuals older than 60 years¹, it will increase in frequency as the population ages. Considering that this epidemiological transition is occurring more rapidly in developing countries², MM will represent a heavier burden in these nations. On the other hand, the introduction of modern therapies such as bortezomib has increased the survival of patients with MM³, thus increasing the need of giving follow-up to long-term survivors. However, these benefits have been mainly observed in developed countries, while regions such as Latin America (LA) have limited access to novel treatments^{1,4}. In Mexico, as in other Latin American countries, there is a need to create adequate epidemiological surveillance tools in order to understand the burden of MM.

Understanding the burden of MM and other rare diseases in LA has been challenging, in part due to the lack of adequate data. Few Latin American countries have national cancer registries and cohort trials⁵. Therefore, data are generally obtained from the World Health Organization and the International Agency for Research on Cancer⁶. However, the Mexican health system is fragmented and has public and private sectors, where populations with different demographic and socioeconomic characteristics are served⁷. The burden of MM would be expected to be variable in Mexican health institutions, given that their target population is highly heterogeneous⁷. Therefore, studies limited to one health institution are probably poorly representative of the complexity of the Mexican health system⁸. In addition, existing data sources exclude information that is essential for understanding MM at the population level, such as complications, stages and treatment response. For these reasons, an exhaustive analysis of the different sectors of the Mexican health system would complement and enrich existing data on the burden of MM in Mexico.

We carried out an extensive analysis of the various sources of information in the public and private sectors to measure the burden of MM in Mexico. We developed a proxy measure for the burden of MM in Mexico using the number of incident and prevalent cases during 2015 and standardizing them to represent the Mexican population structure. In addition, we conducted structured interviews with physicians with experience in the treatment

of MM in Mexico in order to understand clinical characteristics and treatment in the local population.

Methods

To estimate the burden of MM in Mexico, we consulted different data sources corresponding to the private and public health systems for the year 2015. The data on hospitalized patients and outpatients were stratified by gender and age groups (< 20, 20-29, 30-39, 40-49, 50-59, 60 years and more).

MM cases were looked up electronically or by written request. Data sources included institutional yearbooks, institutional statistics' reports, national health information system reports on morbidity and hospitalization statistics, and private institutions health statistics⁹⁻¹³. Total number of MM-specific deaths was obtained from the General Directorate of Health Information^{14,15}. Data related to the structure of the population according to age and sex groups were obtained from the National Institute of Statistics and Geography¹⁶. The National Population Council of Mexico¹⁷ provided updates for the population structure until 2018.

To obtain an approximation of the prevalence of MM in Mexico, we used a proxy variable, given that there are no epidemiological studies or population-based patient registries.

The International Classification of Diseases, tenth revision (ICD-10), was used to identify people with MM. Our prevalence proxy was the total number of people with ICD-10 codes C90.0, C90.1, C90.2 or C90.3 who were provided care during the 2015 period (the full year) by the National Health System. These diagnoses correspond to MM, plasma cell leukemia, extramedullary plasmacytoma, and solitary plasmacytoma. To obtain the prevalence rate for 100,000 person-years, total number of cases in 2015 was divided by the population of each specific age group/100,000 population. To calculate the mortality rate at each age group, the number of deaths of MM in 2015 was divided by the population of each age group/100,000 population. We used the Global Burden of Disease¹⁸ methodology to calculate MM incidence rate. Our rationale for this methodology is that rates' standardization allows a comparison with the health systems of other countries.

Considering that clinical characteristics and treatment of patients with MM are not available in these databases, we interviewed clinical physicians following the Delphi panel methodology¹⁹. After a focused review of the medical literature on MM available up to 2018, we designed an instrument for data collection. The

Table 1. Multiple myeloma. Management according to line of treatment and relapse, and by site of care

Pharmacological treatment for stem cell transplant candidates		
	Public (%)	Private (%)
First-line treatment		
Thalidomide/dexamethasone	44.64	0.00
Bortezomib/thalidomide/dexamethasone	34.09	44.91
Bortezomib/cyclophosphamide/dexamethasone	6.27	33.09
Bortezomib/doxorubicin/dexamethasone	5.64	0.00
Bortezomib/dexamethasone	4.73	4.09
Bortezomib/lenalidomide/dexamethasone	0.00	17.91
Therapy for relapses	34.09	36.36
Bortezomib/dexamethasone	61.00	49.55
Bortezomib/doxorubicin	35.18	30.64
Lenalidomide/dexamethasone	3.82	19.82
Pharmacological treatment for stem cell transplant non-candidates		
First-line treatment		
Melphalan/prednisone/thalidomide	49.55	45.45
Melphalan/prednisone/bortezomib	25.91	22.91
Bortezomib/dexamethasone	15.64	14.36
Dexamethasone/ifosfamide	6.64	12.00
Melphalan/dexamethasone/lenalidomide	2.27	5.27
Therapy for relapses	32.73	32.27
Bortezomib/thalidomide	52.73	46.36
Bortezomib/prednisone	29.55	30.91
Thalidomide/prednisone	17.73	22.73

mean, standard deviation, and 95% confidence intervals were calculated based on surveys. The purpose of this exercise was not to obtain a statistically significant consensus, but rather a qualitative indicator on treatment and clinical status characteristics.

The data obtained using the Delphi panel showed the number of individuals with MM with particular clinical characteristics and specific treatments (Table 1).

Results

During 2015, 2,569 patients with MM were attended to by the Mexican health system (outpatients and hospitalized patients), which corresponds to a prevalence rate of 2.12 x 100,000 population. During the same period, 2,039 patients with MM were hospitalized, with an average number of hospitalizations per patient-year of 1.36. A total of 1,169 patients with MM died during 2015, which corresponds to a mortality rate of 0.97 x 100,000 population (Table 2).

MM incidence rates during 2015 were on average 13% higher in males than in females. Both in males and

Table 2. Multiple myeloma. Attended patients (prevalent), hospitalized patients and specific deaths in Mexico in 2015

	Females	Males
Absolute Cases		
Prevalent cases	1,253	1,316
Hospitalized patients	973	1,066
Hospitalizations	2,766	
Deaths	1,169	
Rates		
Prevalent cases*	2.12	
Hospitalized patients†	2.65	
Hospitalizations‡	1.36	
Mortality§	0.97	

*Attended patients x 100,000 population-year.

†Hospitalized patients x 100,000 population-year.

‡Average hospitalizations per patient-year.

§Specific deaths per 100,000 population-year

females they had a unimodal distribution; the highest were found in people aged 60 years or older (5.2 times the overall average rate), followed by those in adults between 50 and 59 years of age (3.3 times the overall average rate). From 50 years of age onwards, an exponential growth was observed. Those younger than 20 years experienced the lowest MM incidence rates during the study period.

The absolute number of patients diagnosed with MM in Mexico during 2015 was 1,407, which corresponds to a rate of 1.16 x 100,000 population-years. MM incidence rate proportion between men and women was 1.18.

Patients aged 60 years or older were the ones who most used the health system for MM during the study period (Table 3).

Clinically, the vast majority of patients were at stage III of MM (83%). Bone pain and anemia were the most common clinical findings among the individuals (Table 4).

As for MM treatment in stem cell transplantation (SCT) candidates, most private sector doctors preferred to use a combination of bortezomib with other pharmacological agents as first-line treatment. The most widely used regimen by physicians in the public sector was thalidomide/dexamethasone, in contrast to the preference of doctors in the private sector, who added bortezomib to this regimen. Regarding the treatment of relapses, the options used in the public and

Table 3. Multiple myeloma. Attended (prevalent), hospitalized and incident cases according to age group in Mexico in 2015

Patients	Age Group						Total
	< 20 years	20-29 years	30-39 years	40-49 years	50-59 years	≥ 60 years	
Attended							
Absolute cases	28	25	102	402	768	1,244	2,569
Percentage (%)	1.10	0.97	3.96	15.65	29.91	48.41	100
Hospitalized							
Absolute cases	20	18	82	327	526	1,066	2,039
Percentage (%)	0.99	0.88	4.01	16.05	25.79	52.29	100
Incident							
Absolute cases	23	17	61	176	409	721	1,407
Incident rates*	0.05	0.08	0.34	1.16	3.77	5.97	1.16

*Incident cases x 100,000 population-year.

Table 4. Multiple myeloma. Incidence by stage, clinical findings, signs, symptoms and gender, 2015

By stage	I		II		III	
Absolute cases(%)	50 (3.55%)		184 (13.09%)		1,173 (83.36%)	
By clinical-pathological findings	Kidney lesion	Pathological fracture	Bone pain	Tumor	Anemia	Hypoventilation syndrome
Absolute cases (%)	443 (31.48)	669 (47.56)	1,107 (78.70)	48 (3.40)	716 (50.90)	257 (18.24)
By signs and symptoms	Hypercalcemia		Weight loss	Splenomegaly	Hepatomegaly	
Absolute cases (%)	402 (28.60)		245 (17.40)	122 (8.70)	153 (10.90)	
By gender	Females			Males		
Absolute new cases (rate)	662 (1.07 x 100,000 population)			743 (1.26 x 100,000 population)		

private sectors were similar. However, a higher number of doctors in the private sector chose the lenalidomide-dexamethasone combination. The interviewed experts reported similar proportions of treatment regimens for first-line therapy and relapses directed at individuals who were not candidates for SCT. In these cases, a higher number of experts in the private sector preferred using dexamethasone/ifosfamide in comparison with experts in the public sector (Table 1).

There was a high rate of agreement with regard to treatment response by clinical stage between the public and private sectors (Table 5).

As regards the treatment for hypercalcemia, zoledronate was not used in the public sector. Furosemide was used more often in the public than in the private sector. Physicians of the public sector treated anemia more often with iron dextran and did not use darbepoetin as physicians do in the private sector. Private sector doctors

used ganciclovir and valganciclovir as prophylaxis, which was not done in the public sector (Table 6).

Discussion

When patients come into contact with a health institution in Mexico, their diagnosis is recorded according to ICD-10 codes for administrative and management purposes. Using these registries, we constructed a proxy for prevalence and incidence rates. Our proxy was a useful tool to characterize the burden of MM in Mexico. Actually, it corresponds to the prevalence and incidence of detection and medical care of MM cases, since it focuses on records of patients recognized by the health system.

To achieve this goal, we analyzed administrative data from sources that represented the Mexican health system in all its sectors. We believe that our work represents

Table 5. Multiple myeloma. Treatment response according to clinical stage and site of care

	Public (%)	Private (%)
Stage I		
Complete treatment response	40.91	41.18
Partial treatment response	29.09	30.09
Stable disease	18.18	16.91
Progression	7.27	8.64
Non-candidate due to poor general condition	4.55	3.18
Stage II		
Complete treatment response	39.55	37.27
Partial treatment response	25.00	26.45
Stable disease	15.91	15.55
Progression	10.91	11.45
Non-candidate due to poor general condition	8.64	9.27
Stage III		
Complete treatment response	30.09	28.64
Partial treatment response	24.64	23.45
Stable disease	13.73	13.64
Progression	12.64	13.45
Non-candidate due to poor general condition	18.91	20.82

Table 6. Multiple myeloma. Treatment of complications according to site of care

	Public (%)	Private (%)
Treatment for hypercalcemia	38.18	34.55
Alendronate	43.64	59.55
Zoledronate	0.00	18.91
Calcitonin	28.64	12.09
Furosemide	27.73	9.45
Treatment for anemia	36.36	39.55
Erythropoietin	60.45	47.27
Darbepoetin	0.00	41.36
Iron dextran	39.55	11.36
Antithrombotic treatment	31.82	30.91
Low molecular weight heparin	43.64	44.91
Aspirin	37.45	40.45
Warfarin	10.27	10.18
Unfractionated heparin	5.73	4.45
Acenocoumarol	2.91	0.00
Infection prophylaxis	4.45	3.91
IV immunoglobulin	3.64	2.64
Pneumococcal vaccine	2.09	2.36
Influenza vaccine	1.64	1.91
Acyclovir	1.64	1.73*

*Acyclovir/ganciclovir/valganciclovir

higher in males. In addition, people older than 60 years were the most affected by MM. The degree of agreement between public and private institutions regarding MM treatment was high, with very few differences. Agreement was also high for the treatment of complications and for patient clinical characteristics. We discuss our findings in the context of contrasting evidence.

The prevalence rate observed in our study was 2.12 x 100,000 population, while the incidence rate was 1.16. In previous studies on the subject, carried out in Mexico in 2013, an incidence rate of 1.5 was found²⁰. It is highly unlikely that the incidence rate would have decreased in such a short period of time. The lower incidence in our study could be attributed to the use of a different methodology; while our study used various sources of information, previous studies used data from the Global Burden of Disease study²⁰. However, higher incidence rates have been observed in Costa Rica (1.5), Colombia (2.6) and Ecuador (2.3) in comparison with Mexico⁶. Furthermore, the overall incidence rate in South America is 1.7²¹. It should be noted that Hispanic individuals living in the US have a similar incidence to that of Caucasians²². According to available literature, higher access to health services has increased MM detection, which has increased its incidence in recent years¹. For example, in Great Britain, the improvement in case detection resulted in higher incidence rates, in contrast to the incidence rates in Sweden, which remained stable²³. Notably, in the United States, this trend towards an increase in the incidence rate was not observed in Hispanic individuals²⁴. Although MM incidence rates could be influenced by biological differences between Hispanics and other ethnicities²⁵, access to screening programs could also be the cause of the lower incidence rates in Mexico. This is a point where delving deeper is necessary.

The age group with the highest MM incidence rate of was that of people older than 60 years, where we observed a rate of 5.97. An exponential incidence increase according to age was documented in other populations, including Asians²⁶ and Europeans²³. This association pattern is also observed in Latin American populations in general⁶. It is important noting that age-specific incidence rates were much higher in this age group in European populations²³. As the authors explain, a radical change in incidence rates has been observed in this age group, probably due to an improvement in case detection.

The mortality rate we observed was 0.97. Although this figure is comparable with that of other countries in LA⁶, MM mortality in Mexico has increased since 1990²⁰.

the most up-to-date and complete investigation on the burden of MM in Mexico.

The number of prevalent and incident cases, as well as the number of hospitalizations due to MM, was

Part of this increase is due to population aging; however, mortality rates also increased for patients with MM. In this same sense, recent studies show an upward trend in MM-specific mortality in several Latin American countries⁶. The fact that this phenomenon is essentially observed in settings where access to SCT is limited in comparison with the rest of the world stands out¹. Moreover, it should be noted that, in the United States, people of Hispanic origin have higher MM-specific mortality²⁷. Despite the fact that biological factors could impact mortality²⁸, this population also has limited access to SCT in comparison with other populations²⁹. Considering that the development of new therapies has reduced MM-related mortality in developed countries³⁰, it is imperative to understand the determinants of the higher MM mortality observed in the Latin American population.

The authors point at the fact that there were some differences in treatment strategies between the public and private sectors. Lenalidomide was not available in the public sector for the treatment of patients who were candidates for SCT, but it was available for those who were not candidates to it. Ifosfamide was used more often in the private sector. Finally, the combination of thalidomide with dexamethasone was not used in the private sector, but it was preferentially used in patients who were candidates for SCT in the public sector. It should be noted that none of the interviewed physicians used any of the other current treatments for MM, such as carfilzomib and pomalidomide³¹. Our findings confirm that access to new drugs represents a challenge for the reduction of mortality in Latin American countries⁴.

As for the treatment of MM complications, we found a high level of agreement between the public and private sectors. However, zoledronate was not used in the public sector, while it was widely used in the private sector. On the other hand, calcitonin and furosemide were more frequently used in the public sector. This information is relevant, considering that 90% of Mexican patients with MM experienced hypocalcemia in a study conducted in a single center⁸. In addition, darbepoetin was not used in the public sector despite the fact that 10% of Mexican patients had anemia⁸. Acyclovir and valganciclovir were only available in the private sector. Considering that current national guidelines do not include the treatment of complications³², our results highlight the opportunity to standardize them to the reality of the Mexican health system.

The main strength of our analysis lies in the multiplicity of consulted sources, which represent various sectors of the Mexican health system and provide better estimates of the burden of MM. However, there are limitations for a study that was conducted with data that

were not specifically collected for research purposes. For example, it is likely that not all cases could be identified. Furthermore, we were unable to obtain details directly from these administrative sources about the treatments received by the patients. Understanding that prospective cohort studies represent the gold standard for obtaining this information, it should not be forgotten that they are costly, require a lot of time, and, therefore, are not very feasible for rare diseases. Therefore, our proxy measure for MM burden may be useful for epidemiological planning and surveillance purposes. Specially, to better measure, evaluate and manage medical care for cases within the health system and its components. More complete information could undoubtedly be obtained by conducting future studies linking electronic medical record data with national cancer registries or claims to insurance companies.

In accordance with the above, our estimate of the burden of MM in Mexico incorporates the complexity of the National Health System. As access to health services improves, MM incidence rates in Mexico are expected to approach the levels of those in developed nations. Our findings represent an opportunity to strengthen MM epidemiological surveillance in developing nations, as it is the case of Mexico.

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Specific contributions by author

José Ramiro Espinoza-Zamora: study design and conceptualization, data interpretation, writing of the manuscript, extensive participation in reviewing the manuscript and in the preparation process for the selected journal. He has approved the final version.

Rhadames Figueroa-Acosta: writing of the manuscript, extensive participation in reviewing the manuscript. He has approved the final version.

Yusimit de la Caridad Ledesma-Osorio: study design and conceptualization, writing of the manuscript, extensive participation in reviewing the manuscript. She has approved the final version.

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Conflict of interests

The study was carried out with funding from Takeda México, SA de CV, which denies any type of legal liability and/or responsibility deriving from the results.

José Ramiro Espinoza-Zamora denies having any conflict of interest.

Rhadames Figueroa-Acosta was an employee of Takeda México, SA de CV during the study period. Yusemit de la Caridad Ledesma-Orsorio was an employee of Takeda México, SA de CV during the study period.

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