Significant differences in access to tests and treatments for multiple myeloma between public and private systems in Latin America. Results of a Latin American survey. GELAMM (Grupo de Estudio Latino Americano de Mieloma Múltiple)

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ORIGINAL ARTICLE

Significant differences in access to tests and treatments for multiple myeloma between public and private systems in Latin America. Results of a Latin American survey. GELAMM (Grupo de Estudio Latino Americano de Mieloma Múltiple)

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Abstract

The incidence of multiple myeloma (MM) has increased in the last 20 years, particularly in middle and low-middle income countries. Access to diagnostic and prognostic tests and the availability of effective care is highly variable globally. Latin America represents 10% of the world population, distributed in countries of varied size, population, and socio-economic development. In the last decade, great improvements have been made in the diagnosis and treatment of MM. Applying these advances in real life is a challenge in our region. Local data regarding MM standards of care and outcomes are limited. A survey was carried out among hematologists from 15 Latin American countries to describe access to MM diagnostic and prognostic tests and the availability of effective care options. This study provides real-world data for MM in our region, highlighting striking differences between public and private access to essential analyses and therapeutic options.

Keywords Multiple myeloma · Diagnostic hematology · Health care systems · Latin American countries

Introduction

Multiple myeloma (MM) is the second most common hematological malignancy worldwide. Although it remains an incurable disease, the overall survival of patients has doubled in the last decade, reaching a median of 8 years, thanks to novel therapeutic strategies. The incidence of MM has increased in the last 20 years, particularly in middle and low-middle income countries [1, 2]. Access to diagnostic and prognostic tests and availability of effective care vary significantly in the world.

Latin America accounts for 10% of the total world population, distributed in countries that differ in terms of size, population, socio-economic development, and health care resources [3].

There are limited publications regarding hematological diseases in the region. In 2011, Gabús et al. published the results of a study focused on access to diagnostic and prognostic tests and treatments. The authors emphasized that the number of hematologists per inhabitants in Latin America is low (0.9/100,000 inhabitants) and most of the population's health care is provided by government-run public systems (75%). The study highlighted the lack of cytogenetic, molecular biology, magnetic resonance imaging (MRI), or positron emission tomography (PET) scan tests [4].

While international guidelines and reports address how to increase the depth of minimal residual disease detection and how best to use novel drugs, many Latin American countries are struggling to provide adequate basic diagnostic tests and treatment for the disease.

We carried out a survey among hematologists treating MM patients in 15 Latin American countries with the objective of describing access to diagnostic and prognostic tests for MM and the availability of effective care options.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00277-020-03983-x) contains supplementary material, which is available to authorized users.

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This study provides a real-world perspective on MM care in Latin America. We hope that these data will promote a serious discussion on how to enhance equity and access to tests and treatments based on current evidence to all patients with MM in the region.

Objectives

1. To assess the access to diagnostic and prognostic tests and first-line treatment options for MM in LA countries
2. To evaluate differences in diagnosis and treatment between public and private centers

Material and methods

This is a multicenter cross-sectional study. A questionnaire was created including 16 multiple choice and semi-open questions regarding demographic characteristics of participating physicians, centers, and standard of care practices.

All hematologists participating in GELAMM and additional key opinion leaders from each country were invited to participate in the survey. The latter were identified by contacting national Hematology Societies.

The survey was sent through SurveyMonkey to 185 hematologists from 15 Latin American countries (Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Cuba, Ecuador, El Salvador, Mexico, Nicaragua, Paraguay, Peru, Dominican Republic, Uruguay, and Venezuela). The period allocated to complete the survey was from December 2017 to March 2018. An electronic predefined reminder was sent monthly until the closing date to those who had not answered the survey. The survey is shown in the Supplementary Material.

Descriptive statistics and the chi^2 test were used to compare differences between the public and private health systems using the Stata13 software.

Results

We received 109 completed questionnaires (59%) from 13 countries, as shown in Fig. 1: 45 from Argentina (41.3%), 28 from Uruguay (25.6%), 15 from Chile (13.8%), 6 from Paraguay (5.5%), 3 from Peru (2.7%), 2 from Costa Rica (1.8%), 2 from Mexico (1.8%), 2 from Ecuador (1.8%), 2 from Venezuela (1.8%), 1 from Colombia (0.9%), 1 from El Salvador (0.9%), 1 from Nicaragua (0.9%), and 1 from Bolivia (0.9%).

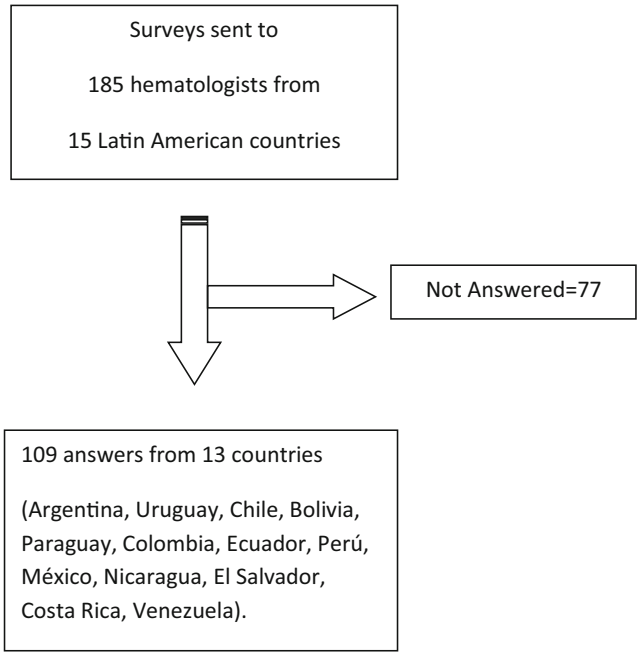

Fig. 1 Survey process flow chart

One-third of the respondents work only in the private sector (35/109) and 10/109 work exclusively in the public sector while the majority (63/109) work in both private and public health care institutions. Sixty percent of responding hematologists work at university hospitals; 64.7% treat benign and malignant diseases, 30% mainly malignant diseases, and 4.9% mainly plasma cell disorders.

Table 1 Availability of diagnostic tests per health care system

Type of test	Public ($N = 89$)	Private ($N = 97$)	P value
SPEP	79.78% (71)	96% (93)	0.0007
IFX	64.04% (57)	90% (87)	< 0.001
sIg	77.53% (69)	94.85% (92)	0.005
sFLC	42.70% (38)	83.51% (81)	< 0.001
uPEP	57.30% (51)	86.60% (84)	< 0.001
uIFX	59.55% (53)	87.63% (85)	< 0.001
Cytogenetics	41.57% (37)	85.57% (83)	< 0.001
FISH	32.58% (29)	67.01% (65)	< 0.001
PC sorting	11.24% (10)	14.3% (14)	NS
CT scan	76.40% (68)	94.85% (92)	0.0003
MRI	55.06% (49)	92.78% (90)	< 0.001
PET-CT	33.71% (30)	79.38% (77)	< 0.001

SPEP, serum electrophoresis; *IFX*, serum immunofixation; *sIg*, serum quantitative immunoglobulins; *uPEP*, urinary electrophoresis; *sFLC*, serum free light chains; *uIFX*, urinary immunofixation; *FISH*, fluorescence in situ hybridization; *CT scan*, computed tomography; *MRI*, magnetic resonance imaging; *PET-CT*, positron emission tomography/computed tomography

Access to diagnostic tests

The availability of recommended tests for diagnosis and staging of MM is shown in Table 1. In public hospitals, > 20% of physicians report having no access to serum protein electrophoresis (SPEP), serum immunofixation (IFX), and quantitation of serum immunoglobulins (Igs) in daily practice; 60% have no access to serum free light chains (sFLC) analysis, either. Moreover, in public hospitals, lack of access to fluorescent in situ hybridization (FISH) testing reaches 67%, computed tomography (CT) scan 23.6%, magnetic resonance imaging (MRI) 45%, and positron emission tomography/computed tomography (PET-CT) 66.3%.

Although most of these tests are carried out in all reporting countries, they are not available in public centers. Only patients that can afford it have access to complete diagnostic evaluation.

In private centers, lack of access to SPEP is < 5%, IFX 10%, Igs 15%, sFLC 16.5%, FISH 33%, CT scan 5%, MRI 7.3%, and PET/CT scan 20%.

Plasma cell sorting is available in 11.2% of the public institutions, and in 14.3% of private centers.

One exception to these findings is Uruguay, where access to tests and therapies is similar in public and private institutions.

Drug access

All physicians reported having access to thalidomide and bortezomib. Autologous stem cell transplant (ASCT) is available in most countries (11/13). Lenalidomide is commercially available in 97.9% (96), melphalan in 92.7% (94), daratumumab in 68% (65), pomalidomide in 67% (57), carfilzomib in 60% (57), and ixazomib in 18% (Table 2). Nevertheless, the commercial availability of these drugs does not mean patients have access to them, as reimbursement issues and local health policies often do not provide them due to their high cost.

As shown in the Addendum, treatment options refer to what is really used by the physicians in daily practice, regardless of the commercial availability of drugs in each country.

Only Argentina and Mexico have participated in clinical trials with novel drugs.

Treatment options for transplant-eligible patients

Bortezomib-based triplets are indicated by 87% of respondents in newly diagnosed (ND) transplant-eligible MM patients in the private setting versus 52.1% in the public system (OR 5.72 (CI 95% 2.32–14.7) $p < 0.001$). More than one-third (39%) of hematologists use cyclophosphamide-thalidomide-dexamethasone (CTD) as frontline regimen in the public setting. High-risk NDMM patients are treated with proteasome inhibitor combinations in all private centers (100%), but only in 74.7% of public institutions ($p < 0.001$). These results are shown in Table 3.

Access to ASCT for patients under 65 years is high (98.2%), yet unavailable in Nicaragua and El Salvador and just recently incorporated in Bolivia. ASCT is fully reimbursed in all private and public health institutions. The main difference, as reported by physicians, is time to transplantation, being there a considerable delay in the public system. Reasons for this delay were not addressed in the survey.

Treatment options for newly diagnosed transplant-ineligible MM patients

The most common first-line option for newly diagnosed MM non-candidates to ASCT is cyclophosphamide-bortezomib-dexamethasone (CyBorD) in private centers and CTD in public hospitals, as shown in Table 4. For high-risk patients, bortezomib-based triplets are the first choice in 86.6% and 64.4% in the private and public settings, respectively (OR 4.09 (CI 95% 1.57–11.16) p 0.01).

In Table 5, we show the cost of original drugs used in MM in some of the participating countries. It is important to notice that several generics are now available in many countries, with an important reduction in cost. These aspects were not addressed in the survey and merit further research.

Maintenance treatment

Almost all physicians (98.92%) prescribe maintenance treatment regardless of age, usually until progression or intolerance (69.9%), or at least for two years (37.6%). Lenalidomide or bortezomib are used for maintenance in the private setting in all reporting countries except for Venezuela. Thalidomide and dexamethasone are the only options available in the public setting in 8 out of 13 countries. Due to high cost or low availability, the approval of lenalidomide and bortezomib maintenance requires a special request form in most countries, which delays the initiation of maintenance treatment.

Discussion

This study shows the challenges faced in the treatment of MM in Latin America. Current evidence shows that early detection and treatment of MM results in better outcomes and prognosis. Therefore, access to adequate diagnostic and prognostic tests should be universal.

Recommended screening tests in monoclonal gammopathies are protein electrophoresis and immunofixation, both in serum and urine, Ig quantitation, and sFLC. Imaging evaluation requires low-dose CT, MRI, and/or PET-CT. Bone marrow evaluation should include immunophenotype,

Table 2 Drugs approved in Latin America for MM patients—2018

	Argentina	Chile	Colombia	Costa Rica	Ecuador	El Salvador	Mexico	Nicaragua	Peru	Paraguay	Uruguay	Venezuela
Melphalan	Y	Y	Y	Y	Y**	Y	Y	N	N	Y	Y	Y
Cyclophosphamide	Y	Y	N	Y	N	N	Y	N	Y**	Y	Y	Y
Thalidomide	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Lenalidomide	Y†	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y†	N
Pomalidomide	Y†‡	Y‡	Y	Y	N	N	Y	Y	Y	Y	Y	N
Bortezomib	Y†	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y†	Y
Carfilzomib	Y‡	N*	Y	N	N	N	Y‡	N	N*	N*	N	N
Ixazomib	Y‡	N	Y	N	N	N	Y‡	N	N	N	N	N
Elotuzumab	Y‡	Y‡	N	N	N	N	N	N	N	N	N	N
Daratumumab	Y‡	Y‡	Y	N	N	Y	Y‡	Y	Y‡	Y	N	N
ASCT	Y	Y	Y	Y	Y	N	Y	N	Y	Y	Y	Y

Y, yes

N, no

† Generic drugs

* Expanded access program available

‡ Approved only for relapsed/refractory MM

** Only intravenous formulation

Table 3 First-line treatment choice for transplant-eligible MM patients

First option	Public system ($n = 67$)	Private system ($n = 85$)
Standard risk patients		
VTD	26.8% (18)	37.6% (32)
CyBorD	23.8% (16)	44.7% (38)
RVd	0	4.7% (4)
KRD	0	0
VCTD	1.5% (1)	0
CTD	39% (26)	13% (11)
TD	7.46% (5)	0
High-risk patients		
VTD	31.3% (21)	24.7% (21)
CyBorD	36% (24)	42.3% (36)
RVd	4.4% (3)	26% (22)
KRD	0	1.1% (1)
VCTD	1.5% (1)	0
CTD	21% (14)	0
TD	1	0
VDT-PACE	1.5% (1)	0
VAD	1.5% (1)	0

VTD, bortezomib-thalidomide-dexamethasone; *CyBorD*, cyclophosphamide-bortezomib-dexamethasone; *RVd*, lenalidomide-bortezomib-dexamethasone; *KRD*, carfilzomib-lenalidomide-dexamethasone; *VCTD*, bortezomib-cyclophosphamide-thalidomide-dexamethasone; *CTD*, cyclophosphamide-thalidomide-dexamethasone; *TD*, thalidomide-dexamethasone; *VDT-PACE*, bortezomib-dexamethasone-thalidomide+cisplatin-doxorubicin-cyclophosphamide-etoposide; *VAD*, vincristine-doxorubicin-dexamethasone

conventional cytogenetics, and FISH analyses. In our study, > 20% of hematologists have no access to SPEP in public centers, less than 60% have access to uPEP, and 60% have no access to sFLC. Accurate diagnosis, prognostic stratification, and follow-up of monoclonal gammopathies are, therefore, deficient and unreliable.

Another problem that emerges from these results is related to the new definition of MM [5]. Centers that do not provide MRI, PET-CT, and sFLC will miss the early diagnosis of MM patients, thus delaying appropriate treatment.

In 2016, the IMWG published the criteria for the evaluation of response to treatment in MM patients [6]. These include SPEP, IFX, and minimal residual disease (MRD) by flow cytometry or next-generation sequencing and PET-CT. According to our results, evaluation of remission status may be inaccurate in many centers due to the lack of access to relevant tests, particularly and most practical nowadays, IFX and sFLC for the assessment of complete remission. Evaluation of MRD as defined by the IMWG criteria is not yet possible in many countries globally, outside clinical trials.

Cytogenetic analysis, both conventional and through FISH, is necessary for risk stratification, not only to define prognosis but also to guide the therapeutic approach [7]. A minority of centers perform FISH testing in the public setting. Moreover, even in the private sector, there is a considerable lack of access to this test (> 30%), and where available, it is performed without adequate plasma cell sorting.

Imaging evaluation has improved substantially, leading to the incorporation of novel techniques in the Myeloma Defining Events criteria. According to our results, more than 50% of patients in public centers have no access to the

Table 4 First-line treatment choice for non-transplant-eligible MM patients

First option	Public system	Private system
Standard risk patients	($n = 66$)	($n = 83$)
VTD	15.1% (10)	12.65% (11)
CTD	34.8% (23)	2.53% (3)
CYBORD	21.2% (14)	36.70% (30)
TD	1.51% (1)	1.26% (1)
RVd	0	2.52% (2)
Rd	8.06% (5)	22.78% (18)
MPT	15.1% (10)	8.86% (7)
MP	1.51% (2)	3.79% (4)
VMP	1.51% (1)	8.86% (7)
High-risk patients	($n = 62$)	($n = 84$)
VTD	17.7% (11)	15.4% (13)
CTD	25.8% (16)	1.2% (1)
CYBORD	25.8% (16)	39.2% (33)
TD	0	2.4% (2)
RVd	4.8% (3)	17.8% (15)
Rd	1.6% (1)	7.14% (6)
VAD	3.2% (2)	0
KRd	0	1.2% (1)
MPT	4.8% (3)	1.2% (1)
VMP	16.1% (10)	14.2% (12)

VTD, bortezomib-thalidomide-dexamethasone; *CyBorD*, cyclophosphamide-bortezomib-dexamethasone; *RVd*, lenalidomide-bortezomib-dexamethasone; *KRD*, carfilzomib-lenalidomide-dexamethasone; *VCTD*, bortezomib-cyclophosphamide-thalidomide-dexamethasone; *CTD*, cyclophosphamide-thalidomide-dexamethasone; *TD*, thalidomide-dexamethasone; *VDT-PACE*, bortezomib-dexamethasone-thalidomide+cisplatin-doxorubicin-cyclophosphamide-etoposide; *VAD*, vincristine-doxorubicin-dexamethasone; *MPT*, melphalan-prednisone-thalidomide

recommended imaging evaluation and are screened using X-rays, which is widely discouraged.

Treatment protocols are conditioned by local reimbursement policies, regardless of drug availability. Even when novel drugs as monoclonal antibodies, second-generation proteasome inhibitors, and novel immunomodulatory drugs are approved and commercially available in several of the reporting countries, patients have no real access to them. Only Argentina and Mexico have had clinical trials with novel drugs in MM.

Unsurprisingly, in the public health system, the most widely used schemes in patients not undergoing ASCT are CTD, followed by CyBorD and MPT, whereas for transplant candidates, CyborD and VTD are the most commonly used treatments. Open access to lenalidomide, however, is more restricted.

Maintenance options are also heterogeneous since novel drugs are used in private centers while no-longer recommended drugs are still used in public settings.

The cost of novel drugs is a concern worldwide, particularly affecting low and middle-low income populations that also have little access to clinical trials. Proper therapeutic strategies are limited, giving rise to an ethical dilemma for the physicians that must treat patients differentially according to the health care provider and reimbursement policies rather than using an evidence-based approach.

By contrast, in most countries included in this survey, ASCT is available for consolidation. In some, however, delay to transplantation is considerable, particularly in the public setting. This is consistent with the results reported by Hungria et al., in which only 27% of ASCT MM candidate patients finally underwent the procedure [8]. Nevertheless, MM is the most frequent indication for ASCT in Latin America [9].

Although not analyzed in the present study, this diagnostic and treatment gap between both systems is likely to be translated into differences in survival, which is greatly concerning. Tarín-Arzaga et al. compared treatment outcomes between the private and public systems in Mexico, showing that MM patients were diagnosed at a more advanced stage and treatment in the public setting did not include novel drugs. Outcomes were clearly better for patients treated in private centers, with a very good partial response or a complete response rate of 65% versus 41% in the public system (p, 0.005) and a median overall survival of 79 versus 41 months, respectively ($p < 0.001$) [10].

Although not all Latin American countries have participated in this study, the information obtained is representative and updated, including real facts faced in public and private centers in Latin America. Due to the nature and aims of the

Table 5 Cost of brand-named drugs in Latin American countries, in United States dollars (USD)

	Argentina	Chile	Colombia	Mexico	Uruguay
Bortezomib 3.5 mg × 1 (Velcade®)	2451.43	954	800	1329	774
Lenalidomide 25 mg × 21 (Revlimid®)	10,245	7567	5000	5820	6145
Carfilzomib 60 mg (Kyprolis®)	6310.76	2670	1350	1317	NA
Daratumumab 400 ml × 1 (Darzalex®)	2503.67	1611	1400	1692	1994
Pomalidomide 4 mg × 21 (Pomalyst®)	11,417.32	11,961	14,000	7770	10,225

NA, not available

survey, no data regarding the response rate and survival were obtained.

Conclusion

Latin America, as a region, is far from complying with the standards for adequate diagnosis and treatment. The ability to diagnose and stratify prognosis in MM patients in public and private centers is widely heterogeneous. Solving inequities regarding diagnosis and prognostic evaluation should be made a priority.

The availability of novel drugs is a more complex situation, affecting treatment access worldwide. An effort should be made to design local approaches that can help reduce the public/private gap. Considering the high availability of ASCT in the region, the first feasible step should be to improve effective access to this strategy in all candidates.

Clinical trials in Latin America should also be encouraged in all institutions. The consolidation of GELAMM, the Latin American group of physicians focused on plasma cell disorders, aims to contribute with local, updated data. It is our hope that this analysis may contribute to increase knowledge about our strengths and weaknesses in the diagnostic and therapeutic approaches and help plan strategies to improve MM care in the region.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval Ethical approvals were obtained at each participating institution.

Informed consent Informed consent was obtained from all individual participants included in the study.

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