Analysis of Availability and Access of Anti-myeloma Drugs and Impact on the Management of Multiple Myeloma in Latin American Countries

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Abstract

Latin American countries represents a large fraction of patients who are treated for multiple myeloma in the world and difficulties of access to new agents and real-world practice are important issues. In this study, we explore areas that impact the availability of anti-multiple myeloma drugs such as health care systems, approval times, coverage of new agents, old drugs, use of generics, and the first-line treatments in 16 nations.

Introduction: Latin American countries (LATAMC) represent a large fraction of patients treated for multiple myeloma (MM) worldwide. In order to understand the difficulty of access to anti-myeloma therapy in LATAMC, we designed this study that explores areas involved in the availability of drugs, such as health care systems, approval times, coverage of new agents, old drugs, use of generics, and the first-line treatments. **Material and Methods:** We collected data from 16 countries in 2015. **Results:** The majority of LATAMC (88%; n = 14) had mixed public and private coverage, with patients with MM cared for in public institutions. Although bortezomib and lenalidomide were approved in 100% and 73% in LATAMC, these figures did not translate to real-world practice as one-half of the nations reported unequal access to the new agents (thalidomide, bortezomib, and lenalidomide) in both public and private systems. Conversely, cheaper old drugs, represented by melphalan, were not available commercially in 44% (n = 7) of nations. Thus, first-line MM treatments for old and young patients in public practice were triplets with thalidomide-alkylating agent-steroid, whereas in private practice, treatments involved bortezomib-alkylating agent-steroid. An alarming rate of 30% of the nations reported suboptimal regimens (eg, VAD [vincristine, adriamycin, and dexamethasone]) or the impossibility of transplantation. **Conclusion:** Our data indicates that bortezomib and transplant are still an unmet medical

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Submitted: Apr 7, 2018; Revised: Jul 4, 2018; Accepted: Aug 6, 2018; Epub: Aug 29, 2018

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2152-2650/$ - see frontmatter
https://doi.org/10.1016/j.clml.2018.08.005

necessity in public systems. In the complex puzzle of myeloma drug access in LATAMC, important issues, such as the adjustment of disparities between health systems, the incorporation of new drugs with an economic cost-effectiveness view, and the re-establishment of essential old drugs, can be a platform to the future.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 19, No. 1, e43-50 © 2018 Elsevier Inc. All rights reserved.
Keywords: Access, Health care systems, Latin America Countries, Multiple Myeloma, New agents

Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of malignant plasma cells in the bone marrow and the secretion of a monoclonal protein in the blood and/or urine associated with common organ dysfunctions, such as osteolytic lesions, anemia, hypercalcemia, and renal failure.[1] In North America, the disease is mostly observed in the elderly (median age at diagnosis, 70 years), and 30,330 new cases are diagnosed each year. In the next 15 years, this incidence is expected to double owing to an increase in life expectancies.[2,3] In turn, in Latin American countries (LATAMC), although few epidemiologic studies have been performed there, it is expected that the number of persons affected by this disease is likely to be higher owing to the larger number of people living in this region. In its geopolitical territory, LATAMC includes 22 nations (the continent plus islands in the Caribbean), and its population is approximately twice that of the United States (US). Multiple myeloma reports from this region examining real-life practice and clinical trials, in both younger and elderly patient populations, have indicated delays in diagnoses and a higher frequency of diagnoses occurring in advanced stages.[4] Furthermore, hypercalcemia at diagnosis was recognized as an independent adverse risk factor for increased mortality, and a higher rate of early mortality must still be addressed.[4-7]

Remarkable progress has been achieved in MM. For example, 18 new treatments have been approved in the past 12 years, including 7 in 2015. These change patient outcomes and life expectancies.[8,9] Initial therapy with triplet combinations incorporating novel agents from different classes of drugs, such as proteasome inhibitors (PI) (bortezomib [Btz], carfilzomib [Cfz], and ixazomib), immunomodulators (IMiDs), thalidomide (Thal), lenalidomide (Len), and, more recently, pomalidomide (Pom), used in association with high-dose therapies with stem cell transplantation (HDT/SCT) for eligible patients, or conventional therapy, melphalan (Mel), cyclophosphamide (Cy), and steroids (Steds) for elderly patients, constitutes the standard of care.[10] Currently, triplet combinations with both a PI and an IMiD are frequently used in the US and in Europe.

In general, approval of a new anti-myeloma agent by a regulatory agency (eg, the US Food and Drug Administration [FDA] or the European Medicines Agency) occurs after it has proven a consistent level of evidence through clinical trials showing an acceptable efficacy-toxicity ratio. Translation to clinical practice will be assured through medical society guidelines and will ultimately be funded by distinct models, for instance, through health insurance companies in the US or by the government in a public system, as is the model in the European Union.[11-13] In contrast, in LATAMC, there is a complex and heterogeneous pathway for novel agents to become available in real life, and the influences of distinct factors, such as economic constraints, the coexistence of different health care models financing oncology treatments, and each nation having its own regulatory agency, make MM treatment practices unique in each of these countries.[6,14]

To understand the difficulty of accessing anti-myeloma therapies in LATAMC, we designed this study to explore different areas involved in the processes of making drugs available in these nations (through 2015), such as health care systems, times to approval, coverage of new agents, availability of old drugs, use of generic drugs and, finally, first-line treatments for myeloma.

Materials and Methods

We collected data using web-based questionnaires focused on the availability of MM drugs in public (government-provided health care) and private (health insurance company) settings, time delays during international approval and incorporation, initial treatment in distinct scenarios (see Supplemental Data in the online version), and the use of generic drugs. We sent the questionnaires to MM reference centers that regularly participate in the Latin American Group on behalf of the International Myeloma Foundation. A total of 16 countries were represented. This study was conducted from October 2014 to March 2015 (Figure 1).

Results

Availability and Access

Participants in this study represented 73% of LATAMC and 92% of the population in all of the South American, North American, and 5 Central American and Caribbean Island nations.

Figure 1 Inquiry Flow Chart Displaying 16 Participating Active Countries From Latin American

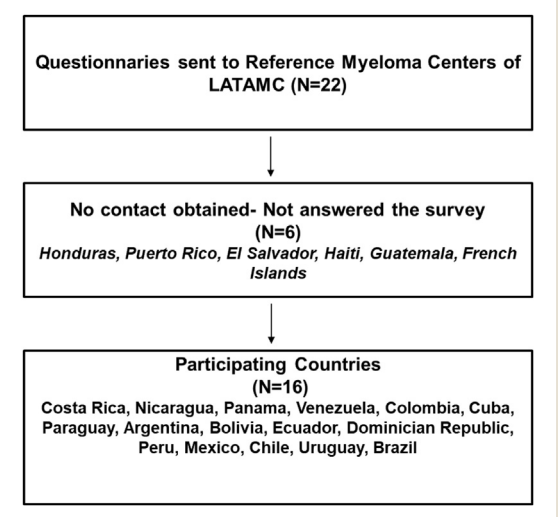
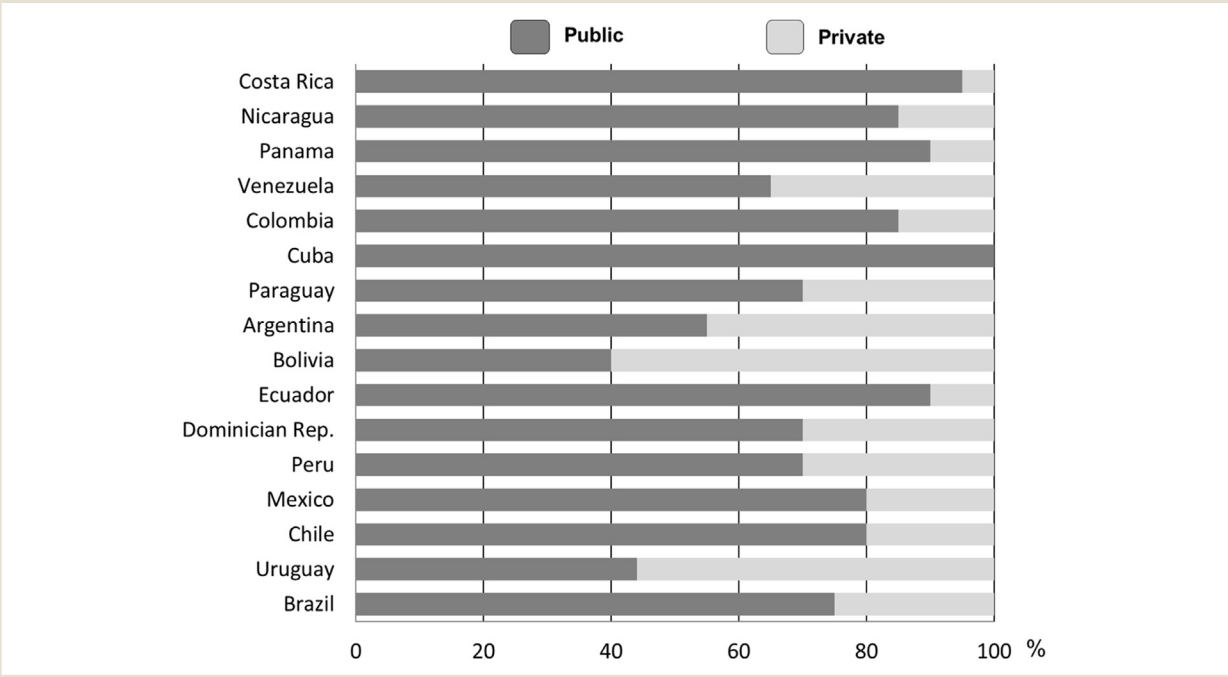


Figure 2 Health Care Systems in Latin American Countries. Distribution of Health Care Systems, in Public Funded by Governments and Private by Supplemental Health Care Companies Among Latin American Countries



Abbreviation: Dominican Rep = Dominican Republic.

Health Care Systems. In evaluating the characteristics of the health care systems, we noted that most of the LATAMC had both public and private systems (92%; n = 15), with a predominance of the former (88%; n = 14). Exceptions included Uruguay and Bolivia, as they had slightly more patients in their private systems, and Cuba, which only had a public system (Figure 2).

Approval. The approval of new agents in LATAMC was handled by regulatory agencies in each country according to local regulations. In 2015, the status of novel agents included full approval for Thal and Btz but only partial approval for Len; approval for Cfz and Pom was rare, and these agents remained unauthorized in many countries. Moreover, using FDA approval of Btz in 2003

Table 1 Approval of New Agents in Latin American Countries in 2015

Country	Thalidomide	Bortezomib	Lenalidomide	Carfilzomib	Pomalidomide
Costa Rica	Y	Y	Y	No	No
Nicaragua	Y	Y	Y	No	No
Panama	Y	Y	Y	No	No
Venezuela	Y	Y	Y	No	No
Colombia	Y	Y	Y	No	No
Cuba	Y	Y	N/A	No	No
Paraguay	Y	Y	Y	No	No
Argentina	Y	Y	Y	Y	No
Bolivia	Y	Y	Y	No	No
Ecuador	Y	Y	Y	No	No
Dominican Republic	Y	Y	Y	No	No
Peru	Y	Y	Y	No	No
Mexico	Y	Y	Y	No	No
Chile	Y	Y	Y	No	No
Uruguay	Y	Y	No	No	No
Brazil	Y	Y	No	No	No

Abbreviations: N/A = information not available; No = drug not approved; Y = yes drug approved for use.

Table 2 Availability of New Agents in Latin American Countries in 2015 in Both Public and Private Systems

Country	Thalidomide		Bortezomib		Lenalidomide		Carfilzomib		Pomalidomide	
	Public	Private	Public	Private	Public	Private	Public	Private	Public	Private
Argentina	Y	Y	Y	Y	Y	Y	Y	Y	No	No
Ecuador	Y	Y	Y	Y	Y	Y	No	No	No	Y
Mexico	Y	Y	Y	Y	Y	Y	No	No	No	No
Costa Rica	Y	Y	Y	Y	Y	Y	No	No	No	No
Venezuela	Y	Y	Y	Y	Y	Y	No	No	No	No
Colombia	Y	Y	Y	Y	Y	Y	No	No	No	No
Uruguay	Y	Y	Y	Y	Y	Y	No	No	No	No
Panama	Y	Y	Y	Y	No	Y	No	No	No	No
Paraguay	Y	Y	No	Y	No	Y	No	No	No	No
Bolivia	Y	Y	No	Y	No	Y	No	No	No	No
Peru	Y	Y	No	Y	No	Y	No	No	No	No
Nicaragua	Y	Y	No	Y	No	Y	No	No	No	No
Chile	Y	Y	No	Y	No	Y	No	No	No	No
Brazil	Y	Y	No	Y	No	No	No	No	No	No
Dominican Republic	Y	Y	No	No	No	No	No	No	No	No
Cuba	Y	–	No	–	No	–	No	–	No	–

Abbreviations: N/A = information not available; No = drug not approved; Y = yes drug approved for use.

and Len in 2005 as a baseline, the mean times for these drugs to be authorized were 3.6 years (range, 1-7 years) and 4.4 years (range, 3-7 years), respectively. The analysis showed heterogeneity among nations with fast and efficient systems (eg, Argentinean approval of Cfz), whereas other cases showed extreme neglect such as the prohibition of Len in Brazil until 2017 (data not shown) (Table 1).

Coverage of New Agents. Even though Btz and Len were approved in 100% and 73% of all LATAMC, respectively, these figures did not translate into real-life use for most patients with MM, and major disparities were observed between public and private health care systems. For instance, a comparison of drug access between the systems showed that, in 50% of the countries, patients did not have equal access to the most-used new agents (Thal, Btz, and Len) in both health care systems (Table 2).

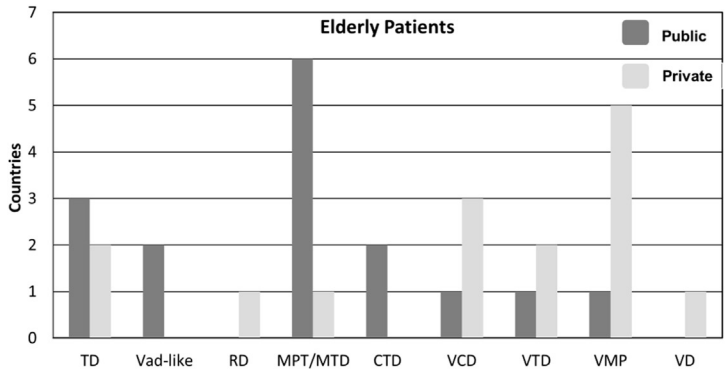
Availability of Old Drugs. Conversely, older classes of drugs, such as alkylating agents (Alk), Mel, and Cy, were not available commercially in oral forms in 25% (n = 4) of nations with public institutions and in 18% (n = 3) of the private systems. In turn, intravenous Mel, an essential and unique drug for MM HDT/SCT, was unavailable in 44% (n = 7) of the public health systems but only 27% of the private systems (n = 4).

Table 3 Generics Use in Clinical Practice of Latin America Countries in 2015

Country	Thalidomide	Bortezomib	Lenalidomide	Carfilzomib	Pomalidomide
Costa Rica	+++	–	–	–	–
Nicaragua	++	++	–	–	–
Panama	–	–	–	–	–
Venezuela	++	++	+	–	–
Colombia	++	+	–	–	–
Cuba	++	–	–	–	–
Paraguay	+++	+	–	–	–
Argentina	–	+	+++	–	–
Bolivia	++	+	+	–	–
Ecuador	+	+++	++	–	–
Dominican Republic	+	+	–	–	–
Peru	+++	+	++	–	–
Mexico	++	+	++	–	–
Chile	–	–	–	–	–
Uruguay	+	+++	++	–	–
Brazil	+++	+	–	–	–

Abbreviations: – = Never; + = rarely; ++ = frequently; +++ = always.

Figure 3 First-line Multiple Myeloma Treatment for Elderly Patients Among Public and Private Health Systems in Latin American Countries in 2015



First line	Public (n=16) n, (%)	Private (n=15) n, (%)
Suboptimal TD, Vad-like	5, (31)	2, (13)
Len-based RD	0, (0)	1, (7)
Thal-Alk-Steds MPT, CTD	8, (50)	1, (7)
Btz-based VCD, VTD, VMP, VD	3, (19)	11, (73)

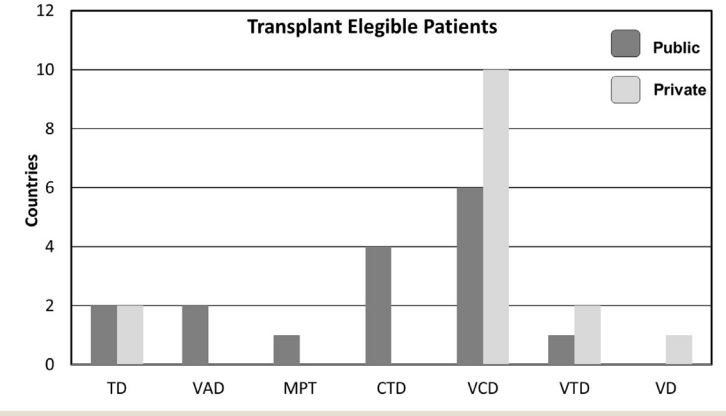
Abbreviations: CTD = cyclophosphamide, thalidomide, and dexamethasone; MPT = melphalan-prednisone and thalidomide; MTD = melphalan, thalidomide, and dexamethasone; RD = revlimid and dexamethasone; TD = thalidomide and dexamethasone; Vad-like = vincristine, adriamycin, and dexamethasone; VCD = velcade, cyclophosphamide, and dexamethasone; VD = velcade and dexamethasone; VTD = velcade, thalidomide, and dexamethasone.

Use of Generics. The next step was to investigate the use of generics, or biosimilars, of the new agents in clinical practice in LATAMC. To explore this issue, the questionnaires asked about the presence of specific drugs and the frequencies with which each was used in each nation. The total proportion of generic use was Thal: 81%; BTZ: 75%; Len: 40%; and for Cfz and Pom, none. Interestingly, each drug approval had a distinct profile; for example, Thal was almost always non-marketed and generic, BTZ was marketed and rarely generic, and Len was marketed but was frequently used as a generic (Table 3).

Treatment of Multiple Myeloma in LATAMC

Front-line Treatments. In the public systems, the first-line treatments for elderly patients were triplets with Thal-Alk-Steds in 50% (n = 8) of the countries, Btz-based combinations in 19% (n = 3) of the countries, and suboptimal regimens (eg, Thal and dexamethasone [TD] and vincristine, adriamycin, and dexamethasone [VAD]) in 31% (n = 5) of the countries. In young patients, the distributions of induction treatments before receiving transplants were Btz plus Alk or Thal and Steds in 45% (n = 7) of the countries, Cy, Thal, and dexamethasone (CTD) in 25% (n = 4) of the countries, and suboptimal regimens (eg, VAD, TD, or Mel-prednisone and Thal [MPT]) in 30% (n = 5) of the countries. When evaluating the same countries' practices in their private systems, the numbers changed, and Btz-based regimens were the most frequently used for both elderly and young patients in 74% (n = 11) and 89% (n = 13) of the nations, respectively. In addition, lower rates of suboptimal therapies of approximately 10% were observed (Figures 3 and 4).

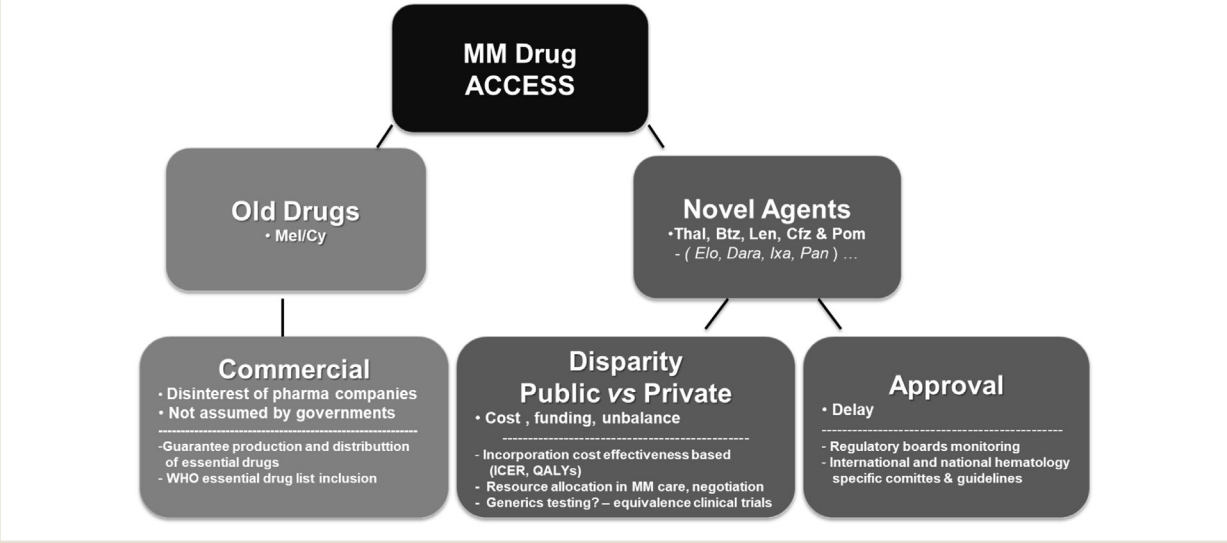
Figure 4 First-line Multiple Myeloma Treatment for Transplant-eligible Patients Among Public and Private Health Systems in Latin American Countries in 2015



First line	Public (n=16) n, (%)	Private (n=15) n, (%)
Suboptimal TD, VAD-like, MPT	5, (30)	2, (11)
Thal-Alk-Steds CTD	4, (25)	0, (0)
Btz-based VCD, VTD	7, (45)	13, (89)

Abbreviations: CTD = cyclophosphamide, thalidomide, and dexamethasone; MPT = melphalan-prednisone and thalidomide; TD = thalidomide and dexamethasone; Vad = vincristine, Adriamycin, and dexamethasone; VCD = velcade, cyclophosphamide, and dexamethasone; VD = velcade and dexamethasone; VTD = velcade, thalidomide, and dexamethasone.

Figure 5 Challenges for LATAMC for Myeloma Drug Access in 2015 and Future: Main Problems and Possible Solutions. Summary of Main Barriers to Access of Anti-myeloma Drugs in Latin American Countries and Possible Solutions



Abbreviations: Btz = bortezomib; CFZ = carfilzomib; Cy = cyclophosphamide; Dara = daratumumab; Elo = elotuzumab; ICER = The Institute for Clinical and Economical Review; Ixa = ixazomib; Len = lenalidomide; Mel = melphalan; Pan = panabinostat; POM = pomalidomide; Qalys = quality-adjusted life years; Thal = thalidomide; WHO = World Health Organization.

Stem Cell Transplantation Practice

Even though the study was not designed to specifically evaluate transplant practices, it was possible to obtain reports on them from most LATAMCs. Bolivia and Nicaragua declared it impossible to perform transplants owing to a lack of investment in structures needed to manage the complexity of a bone marrow transplant, such as the availability of blood bank facilities (eg, leukapheresis capabilities) and cryopreservation technology. In turn, most nations' public systems were unable to attend to the major demands of transplant procedures efficiently, and consequently performed them with an inappropriate delay of greater than 1 year after induction or lost transplantation opportunities altogether. Recently, a lack of production and distribution of Mel in intravenous form also played a role in transplant delays (eg, in Brazil). Furthermore, Mexico reported a permanent absence of this drug in its public services and used a high dose of oral Mel with transplanted patients to circumvent this issue.

Discussion

Recently, it was reported that there has been more progress with treatments for myeloma than for any other cancer; this demonstrates the impact of novel drugs and changes the natural history of the disease.[9,10] However, this progress is not reflected in current practice in LATAMC, and a lack of access to treatments that follow the standard of care remains a challenge for many nations. Our study showed a singular profile of health systems in which public and private health care systems coexist, with the majority of patients utilizing public institutions. As a result, the presence of this duality resembles the private model in the US and the public model in Europe, generating different realities of MM treatment in each country.[15]

Clearly, the study shows an unbalanced distribution of anti-myeloma drugs, because only Thal was available for most patients in LATAMC receiving care in public systems, whereas Thal, Btz, and Len were used in private systems. Curiously, Thal availability was mainly a coincidence, as this availability is a heritage of the production of the drug for leprosy programs. As a result, it was freely supplied by governments and not commercialized. This public reality should be urgently addressed, not only owing to its inefficiency but mainly owing to its violation of the basic principle of equality. Although there are many factors involved, this situation can be partially explained by profound socioeconomic inequalities that originated in the colonial period and continued until the 20th century processes of capitalist modernization generated limited social redistribution. Furthermore, various LATAMC developed segmented social protections and health systems tied to formal labor markets that excluded the majority of the population owing to high levels of unemployment or people's work not being linked to governments or companies.[16]

On the other hand, global concern is raised regarding the current situation of progressively increasing costs for innovative anticancer therapies being set by pharmaceutical companies. For nations with economic constraints, it is an alarming issue that leads to a lack of access to these drugs, and emergency measures should be taken to guarantee treatment for those with MM in these nations that are fair and that follow the standard of care.[17,18] However, the absence of essential drugs could not be explained completely by this factor, because in our study, we found that the cheaper drugs for MM management, such as Alk, were also not available. Importantly, the absence of Mel in intravenous form in one-half of the public institutions in LATAMC reported here was implicated in the reduced number of transplants completed and the reduced use of standard-

of-care triplet MPT for elderly patients.[6] The authors believe that there are multiple reasons for this issue, such as disinterest by pharmaceutical companies and an absence of investment by public health boards to ensure basic care for MM that guarantees the standard of care (eg, manufacturing Alk).[14] As a matter of fact, from our knowledge, MM is not currently internationally protected as a disease, and its therapeutics are not on the essential drugs list for cancer created by the World Health Organization.[19] Even with the low prevalence of MM compared with solid tumors, it represents the second most common hematologic malignancy in the hematology field, and thus, there should be a fundamental acknowledgment of this disease and inclusion of the sine qua non drugs (eg, Mel and Btz) on the list.[20-22] This inclusion could serve as a guideline to promote good medical practices in order to help with its incorporation, promote health, and reduce disparities in MM treatment in low- and medium-income countries.[23]

Our study showed a delay of 3 to 4 years for the approvals of Btz and Len since first being released by the FDA, and this contributed to a lack of access to these new drugs for MM treatment in LATAMC.[24-27] However, the authors recognize that new drug approvals are occurring more quickly. Recently, Brazil's National Health Surveillance Agency (ANVISA) approved second-generation PIs and monoclonal antibodies (eg, daratumumab) for relapsed patients. Daratumumab was also released for newly diagnosed MM in combination with Btz, Mel, and prednisone. Nevertheless, this raises concerns about an increase in the disparity between treatments in public and private systems in LATAMC, with new treatments only being provided and affordable in private care that excludes the majority of patients.

A proactive solution could be to link all high-cost new drug approvals to a uniform national program of progressive preplanned incorporation. This would involve the participation of medical societies and would be supported by evidence-based guidelines and professional health administrators from both public and private systems. Nongovernmental organizations would represent patients and pharmaceutical companies; altogether, this would guarantee open information and access to all citizens. On the other hand, new incorporations should be meticulously studied to understand the real impacts that the actions would represent in terms of cost burdens on health systems, and room should be created for negotiations. In this regard, different national variables, such as demographic and economic ones, should be accounted for when estimating the number of patients to be treated and the Gross Domestic Product.[28] Another important action to LATAMC would be to approve effective low-cost anti-myeloma protocols, including old and new agent drug combinations and planning regional collaborative clinical trials with this objective.[29]

In real life, 2 different treatment regimens containing or not containing Btz were applied in the same nation, and the main driver of this difference was in patients having or not having supplemental health insurance. Thus, despite being globally approved in LATAMC, Btz access was restricted to a smaller fraction of patients who were mostly receiving care in private systems (eg, young: velcade, Cy, and dexamethasone [VCD] and unfit: Btz (velcade ®), Mel, and prednisone [VMP]), whereas public systems used Thal-Alk-Steds combinations (eg, young: CTD and unfit: MPT). Moreover, our study showed an alarming rate of suboptimal treatment in the public systems in up to 30% of nations.

For a long time, HDT/SCT and Btz were proven to be cost-effective using different evaluation tools, such as the Quality-Adjusted Life Year (QALY) and the Institute for Clinical and Economical Review (ICER).[30] Undertreatment or irregular savings with essential drugs can be catastrophic in this disease, increasing patients' risks from standard to high risk and increasing health expenditure owing to long hospitalizations, orthopedic surgeries, dialysis, and chronic disabilities.[31-33] On the other hand, not all novel drugs marketed for myeloma proved to have the expected benefits in post-market and community studies, and their incorporation by countries with fragile economies should be handled judiciously.[34] As a matter of fact, one of the solutions used by some countries, increasingly in LATAMCs, is the use of biosimilar drugs. Interestingly, the insertion of PIs was performed using velcade, whereas second-generation IMiDs used generic Len. Recently, this figure changed, and generic Btz has dominated in most countries since at least 4 distinct laboratories began competing for this market.[35-37] However, an evaluation of patent breaking was beyond the objectives of this study. We noticed heterogeneity among health regulations in these nations, with variations that ranged from it being a forbidden practice in some to a formal procedure in others.

Conclusion

Unsurprisingly, the MM treatment picture in LATAMC until 2015, and to an extent to the current time, indicates that a lot of effort needs to be made in this field to guarantee equal outcomes in public settings. Transplants and Btz are still an unmet medical necessity despite being the standard of care for more than 15 years. For the first time, the availability of drugs in LATAMC was reported, and we hope that these data will be helpful in examining the main problems and will serve as a platform for improvements in distinct areas of this complex puzzle of myeloma drug access that has potential solutions (Figure 5). Finally, we expect that basic care for MM will overcome barriers of geographic frontiers and social status and reach all patients who need therapy for it.

Clinical Practice Points

- MM in LATAMC was previously reported in different observational publications regarding clinical characteristics at diagnosis, prognosis systems such as Durie-Salmon and ISS staging systems, and some information about treatments and outcomes. However, until now, the access to anti-MM drugs, first-line treatments and the main common problems regarding undertreatment were largely unknown or not reported among these nations.
- We pooled together the information of 16 LATAMC nations from MM reference centers participating in the Latin American International Myeloma Foundation. This study showed that MM treatment had mixed public and private coverage, with most of MM patients cared for in public institutions and with great disparities of essential treatments inside the same nation. Clearly, standard of care practices such as bortezomib and transplantation are not given for most patients, and suboptimal

treatments reached 30% of the nations in public institutions. This influence generated different choices of first-line treatments in the countries, with public treatments using Thal-containing regimens whereas private treatment used Btz. In spite of regional constraints, the cheaper availability of old drugs also remains a problem, disrupting the management of fit patients in transplant practice and elderly treatment combinations (eg, MPT).

- Our data showed, for the first time, the real-world MM practices in LATAMC, dissecting the main regional problems involving access to essential drugs and serving as platform for improvements in MM care in the future.

Disclosure

Roberto José Pessoa de Magalhães Filho participates as speaker in Brazil for Takeda, Janssen, Amgen, Celgene, and BMS; Roberto José Pessoa de Magalhães Filho participated as board advisor in Brazil for Takeda, Janssen, and Amgen. The remaining authors have stated that they have no conflicts of interest.

Supplemental Data

Supplemental data accompanying this article can be found in the online version at https://doi.org/10.1016/j.clml.2018.08.005.

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