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Citation: Cristina Gutierrez Delgado, Virginia Abello, Martha Alvarado et al. Challenges and Opportunities to Access Innovation in Latin America: The Case of Combination Therapies for Multiple Myeloma

Abstract:
Purpose: To address the barriers limiting access to combination therapies (CTs) in Latin America (LA), specifically for patients with multiple myeloma (MM), alongside a roadmap to address them.
Methods: A panel of LA experts was provided with relevant questions to address in a multi-day conference. Responses were discussed and edited by the panel through numerous drafts and discussions until consensus was achieved.
Results: The authors identified challenges in CT access in MM in LA and proposed suggestions to address these, including health technology assessment frameworks that assign value to each constituent, adapted legal structures enabling collaborative pricing negotiations, and innovative pricing and contracting mechanisms. These challenges and suggestions apply to CT for other oncologic diseases.
Conclusion: Increasing CT access demands concerted efforts from all stakeholders. As regulatory and pricing barriers persist, a great need exists to increase CT access in LA. These suggestions can serve as a roadmap for CT adoption in other countries.
Keywords: Latin America; combination therapy; multiple myeloma; value attribution, HTA, access, pricing; reimbursement.

Introduction:
Cancer represents one of the greatest public health and economic issues worldwide, with an increasing burden due to population ageing and growth (1). Likewise, the costs of cancer care, especially pharmacotherapy, are increasing. Its complex nature and the adoption of precision medicine have fostered the exponential development of combination therapies (CTs). CTs have become the standard of care for most hematological malignancies, rendering equity in access and reimbursement fundamental to providing quality care and improved outcomes. Lack of access to new technologies and high-cost medications, an intricate issue where economics, medicine, health policies, and ethics intersect, threatens the sustainability of healthcare systems globally. This is particularly true in the emerging economies of Latin America (LA) where according to the World Health Organization (WHO), 50% of the population does not have access to high-cost drugs (2). Challenges in providing access to CTs include uncertainty at the time of market authorization, limited adoption of value-based pricing and contracting models, a lack of health technology assessment (HTA) frameworks for value attribution to each CT, and inflexible legal frameworks that limit collaborative price negotiations between CT manufacturers. This paper will analyze the challenges surrounding CT in LA, using multiple myeloma (MM) as a case study and provide possible strategies and solutions that address these issues.

Methods
To address the above issues, the Americas Health Foundation (AHF) conducted a literature review to identify scientists and clinicians from LA who have published in MM or health economics for CT (see Box 1). PubMed and Embase were used to identify clinicians and scientists with an academic or hospital affiliation, and who had published in these arenas since 2015. Augmenting this search, AHF tailored a list of individuals suitable for the project that could create Region-specific recommendations. As a result, AHF convened an eight-member panel of LA experts in MM and HEOR.
To better focus on the discussion, AHF developed specific questions to address the salient issues on the subject for the Panel to address. Subsequently, a written response to each question was drafted by individual Panel members and each narrative was edited by the entire group through numerous drafts and rounds of discussion until complete consensus was obtained. During the meeting, each question was discussed at length and consensus for each topic was established. The Panel reviewed the document after the consensus to again acknowledge that they were in full agreement.

LA health systems and regulatory processes
LA faces several challenges in timely access to healthcare in general, including ineffective delivery of care and slow uptake of policies that improve efficiency, equitable access, financing, and management. While all LA countries strive for universal health coverage, this does not always translate to practice and there are significant differences in access within and between countries, especially regarding high-cost and innovative treatments. LA health systems generally contain several subsystems and serve highly heterogeneous populations, geographic locations, and socioeconomic statuses. These complex systems rely on multiple stakeholders and an intricate interplay between private and public sectors, which add a layer of complexity to effective patient access to new technologies (3-5). A fiscal gap of 1.1-2.9% exists between public spending on health of the gross domestic product (GDP) and the benchmark health spend of 6% of the GDP, recommended by the WHO, with only Costa Rica, Uruguay, and Colombia meeting the benchmark (6). As a result, high out-of-pocket expenses are common (as high as 41% in Mexico) (7).

For Argentina, Brazil, Colombia, and Mexico, Table 1 presents an overview of the HTA landscape with the stakeholders involved in regulatory, pricing, and reimbursement.

In LA, patients with MM experience diagnosis delays exacerbated by lack of awareness in the primary care setting, initial misdiagnosis, and inefficient referral systems (8-9), which often result in more advanced stages at diagnosis (10-11). Once diagnosed, limited drug access presents major challenges to providing standard of care treatment, especially in the rapidly evolving treatment scenario of MM (12-13). Further, there are vast inequities in drug access between the public and private systems, with the former often excluding or restricting essential anticaner drugs (14). Data from 16 LA countries regarding MM treatment patterns and drug access show that bortezomib and lenalidomide were approved in most countries, but had unequal access, particularly between the public and private systems. Most patients in the public health system received thalidomide-based treatment, while bortezomib combinations were the standard in private practice (15). For instance, the Grupo de Estudio Latino-Americano de Mieloma Múltiple (GELAMM) found significant differences in survival between public and private system patients. Those in the public system were more symptomatic at diagnosis, had more advanced disease, and less frequently received bortezomib-based induction therapy, autologous stem cell transplantation (ASCT), or maintenance therapy (16).

MM in the context of CT
MM is a heterogenous plasma cell disorder that weakens the immune system and generates a wide range of symptoms that complicate early diagnosis and timely treatment (17). It represents a growing burden, with a 126% increase in global incidence in the past 25 years (18). Robust epidemiological data for LA are scarce and fragmented; therefore, these data may not represent national realities. The estimated age-standardized incidence rate (ASIR) is 1.7/100,000 in LA, placing MM within the range of rare diseases (19). According to Globocan, in 2020, ASIRs for MM are: 2.0 in Brazil and 2.2 in Colombia. Further, the LA reported median age at diagnosis is lower than in other regions (20). Global trends exhibit a decrease in mortality and increase in overall survival (OS) due to treatment advances; however, LA data show increasing mortality in several countries, partially explained by the limited access to international standards of care (13, 21-22).

MM standard of care
The multiple subclones often present at diagnosis and clonal evolution during therapy contribute to treatment resistance and refractory disease in patients with MM. CT with different agent classes is the best strategy to target multiple clones and combat the emergence of drug resistance (23-24). New agents in CT have allowed physicians to design personalized treatments; however, the vast new data available require precise and objective analysis (25). In MM, CTs can be composed of doublet, triplet, or quadruplet regimens. The latter two produce better outcomes, including minimal residual disease (MRD) negativity and progression-free survival (PFS), treatment response, time to next treatment, and overall response rate, among others in most MM patients. While these findings may translate into improved overall survival (OS), longer follow-up times are required due to the duration of treatment and prolonged survival (26-30). Box 2 lists the standard of care options for patients at various stages.

CT availability and accessibility
Among hematologic cancers, MM is one of the conditions with the most regulatory approvals in recent decades, evidencing the tremendous innovation available for patients. The United States’ Food and Drug Administration (FDA) has approved the following drugs: proteasome inhibitors (bortezomib, carfilzomib, ixazomib); immunomodulators (thalidomide, lenalidomide, pomalidomide); monoclonal antibodies (elotuzumab, daratumumab, isatuximab); HDAC inhibitors (panabinsonostat); and more recently, venetoclax, selinexor, belantamabmafodotin, melfuflen, and idecabtagenevicleucel (ide-cel) (31-32).

Not all treatments are currently approved or available in LA, and once approved, access depends upon socioeconomic status, geographic location, affiliation to a private or public system, and patient profile. If regulatory approval is not the most critical barrier, certainly access is. Timely access to innovative CTs in public systems is severely lacking. For example, even though bortezomib was approved in 2003 by the FDA and in 2005 by the Brazilian regulatory agency (Agência Nacional de Vigilância Sanitária (ANVISA)), Brazil did not incorporate its use into the public system until September 2020 (33). These severe delays are commonplace in most LA countries.
Another challenge lies in determining the appropriate sequence of MM treatment in resource limited settings, in part because clinical practice guidelines (CPG) provide all acceptable treatment options but generally do not provide locally adapted recommendations on the most cost-effective care. The possibilities of CTs are in direct proportion to the availability and access to the approved drugs. For example, the disparities that exist in the treatment of lenalidomide-refractory patients are an unmet need in MM worldwide due to shorter PFS compared to non-refractory patients. To address this unmet need, combination treatment with monoclonal antibodies, second generation Pls, pomalidomide, or innovative treatments are proposed worldwide. Nevertheless, these CT options are rarely and inconsistently available in LA, which further exacerbates the problem.

Clinical trials provide early access to innovative therapies and alternative sources for diagnostic tests, proving to be valuable in cancer care improvement strategies. Successful clinical trials for CTs underline the urgent need for access to new oncologic drugs. Real-world data (RWD) on treatment outcomes in LA are scarce; CTs for MM are no exception (34). Insufficient local data prevent value-based methodologies in the assessment of novel CTs (35), proper of outcome monitoring, and complicates determining the population’s epidemiologic characteristics. Additionally, RWD sources are necessary to explain discrepancies between clinical trials and clinical practice, scale the impact of approved drugs, and address some of the uncertainties inherent in assessing efficacy, safety, and cost-effectiveness associated with CTs. Even when the number of patients receiving continuous first-line treatment with Pls, lenalidomide, and daratumumab increases, there will be a need for more innovative drugs in subsequent relapses. Table 2 lists treatment option in first line and at relapse in MM patients in LA and coverage within public and private healthcare systems in Argentina, Brazil, Colombia, and Mexico.

**Systematic access barriers to CTs**

Improved access to quality MM care in LA requires many systematic issues to be addressed, including strengthening early diagnosis, implementing a multidisciplinary approach to ensure comprehensive care, and breaching disparities between public and private healthcare systems (10, 14). Further, financial planning would benefit from long-term vision, often lacking in LA health systems, to ensure resource allocation is based on disease burden and value-based care. Access to high-cost cancer drugs represents only one aspect in this monumental challenge. The specific limitations to improving access to CT are outlined below.

The highly fragmented healthcare systems in LA cause disparities in coverage and access to new technologies, including CTs, in regulatory approvals, lower capacity for price negotiation under anti-trust legislation, and coverage gaps between the public and private systems. From a systemic perspective, such fragmentation causes inefficiencies and precludes coordination (34, 46). The high cost of CTs coupled with increased treatment duration due to improvements in PFS and OS could pose a challenge for medium- and long-term financial sustainability for health systems, since more patients will require these therapies for a longer period of time (47). To strive for sustainability, the entire patient journey must be considered in evaluating the impact of initiating treatments at different disease course points based on value (34, 48).

**Challenges in assessing the value of CTs**

From payers’ and policymakers’ standpoints, CTs include two constituents that make up the combination: the “backbone therapy” and the “add-on therapy,” which is the asset driving clinical trials and requesting the label indication. The constituent therapies may be owned by the same or different company. The types of combinations are described in Box 3 (49).

The major challenges in assessing the true value of CTs is that current HTA frameworks are not adapted for CTs and often yield counterintuitive results. This may be because they do not use differentiated criteria for assessment, no specific mechanisms exist to attributing added clinical benefit to constituent therapies, and conventional cost-effectiveness analyses deem add-on therapies as not cost effective (even at zero cost) due to the incremental costs of the backbone therapy as the treatment duration increases (49).

The ISPOR HTA LA Roundtable at which participants analyzed the use of value-based pricing (VBP) in six LA countries (36) identified the following additional obstacles in value appraisals of CTs: the disease stage as CTs added value changes accordingly; financial incentives, occurring more often in the private system, where both products are reimbursed but the mechanism of payment, “fee-for-service”, favors the use of the more expensive products; and ensuring an appropriate competitive environment that includes generics and biosimilars (34). These challenges must be addressed comprehensively as they are intertwined.

**Capturing value attribution**

Capturing the actual value attribution (i.e., clinical benefit) of the CT in relation to other therapies is a major challenge faced during clinical trials and once the CT is incorporated to the clinical practice (50). When assessing value, it is important to consider two key concepts that explain the relative performance of the components: the amount of additional value generated by the combination in comparison with their independent use as monotherapies and the relative change in survival vis-à-vis the relative change in duration of treatment (51).

In terms of additional value, most CTs show that the health gain provided by the two separate monotherapies is greater than that of the monotherapy but still less than the health gain provided by the two treatments when used in combination. Therefore, the treatments in combination render the greatest health gain. To address this fact, it is necessary to agree upon new principles for value appraisal to recognize the individual value of each monotherapy and the contribution to the CT. Among the principles that are under discussion by HTA experts are the universality of application to diverse types of technologies, including CTs, the logic and symmetry to be applied to the components, as well as completeness to fully attribute the value of the CT between its components (51).

Add-on vs backbone head-to-head clinical trials represent the most challenging scenario for value assessment, given the nature of the incremental cost of the add-on, not only in terms of its
promotes the reassessment of the backbone therapy is necessary (49).

**Strategies to improve CT assessments**
As CTs are the standard of care for MM and other cancers, it is imperative that HTA methodologies adjust to the complexities of assessing them. For the past 40 years, the basis of healthcare technology has shifted significantly. While effectiveness and safety are still the paramount aspects of this decision-making process, the economic evaluation of the technology, through cost-effectiveness, cost-benefit analysis and budget impact study, has become an important component of HTA. This evolving process suggests that to strengthen the HTA framework and include all stakeholders involved in cancer care (patients, payers, patient advisory groups, pharma companies, policy makers, academia, key opinion leaders (KOLs)), it becomes crucial to include measures that capture the patient perception related to CT treatments such as quality of life, patients reported outcomes and social impact.

**Value-based assessment**
In practice, the use of CT can be assessed under a value-based methodology. In health systems where value assessment focuses on added clinical benefit, the magnitude of improvement offered by CTs can be captured through indicators, such as the median PFS, OS, MRD, and/or ORR. These indicators also can differentiate between “transient” treatments and continuous ones, as is the case of MM where the OS has more than doubled in the past 15 years (34). In health systems where decision-making for inclusion of new technologies highly influenced by cost-effectiveness and budget impact, specialized indicators such as value extension, insurance value, real option value, and value of hope can be used (49). However, implementing these indicators in real life is challenged by data availability and complexity (49). This HTA framework encourages assessment and pricing adapted to specific treatment stages because the added values are not the same at each point in the patient journey (23-24). For example, in MM, a CT’s clinical benefit may be more pronounced in the early lines of therapy compared with the relapsed setting (55). The methodological adjustments required are feasible, given the maturity of the LA HTA systems (56). The proposed multicriterial measurement for CTs are described in Box 4. Of note, the recommended indicator should be developed for each CT that will be compared (57-62). Traditionally, HTA are based solely on efficacy but the promise that RWD holds may improve effectiveness (63). Adjusting the original HTA methodology and design is necessary to better capture true value, because the current structure does not fully recognize the benefits of CTs. Figure 1 outlines an alternate strategy for HTA of CT.

**Challenges to pricing, contracting, and procuring CTs**
Given the particularities of CTs for MM, alternative pricing and payment models should be considered, focusing on how these approaches can improve patient access, market uncertainty, and budget allocation. The following key obstacles have been identified to pricing, contracting, and procuring CTs: enforcement of antitrust and competition regulatory frameworks; intellectual
property rights ownership of the components; and lack of data to use VBP strategies (34, 65). Additional procurement challenges arise from current tender regulations and methodologies that focus mainly on price per month or up-front costs, leaving little room for value-based approaches. These methodologies could benefit from a shift to long-term vision and understanding value as clinical benefit. Addressing these obstacles requires strong coordination among the multiple stakeholders involved in the pricing/reimbursement processes and adjustments to applicable regulations.

Antitrust/competition legislation
Antitrust legislation can increase costs, especially of multi-branded CTs, because there is limited ability for negotiation and arbitration between manufacturers. The absence of such produces inefficiencies in price adjustments for CTs and can generate budgetary tensions for payers who, to reduce spending, may choose to restrict patient access to CTs and/or decrease the price they are willing to pay the manufacturer. Either of these can result in decreased investment in R&D in the mid- and long-term, resulting in fewer treatment options and, thus, reducing the life-years gained and the opportunity to obtain greater outcomes and access to new technologies (49). In general, legislation regarding antitrust practices aims to strengthen competition among manufacturers. However, antitrust frameworks fail to reduce CT prices because typically CT constituents are either under the patent period or because it is manufactured by a single source, even after the patent expires (34, 36). An example of successful antitrust immunity is the airline industry where alliances can be formed to jointly set fares to the consumer’s benefit due to increased pricing efficiency. This is demonstrated by data that shows high fares for routes where there are fewer independent competitors (66).

Improving the pricing, contracting, and procurement environment to lower treatment costs, improve coverage, and increase CT access, updating legal and regulatory frameworks regarding negotiation between manufacturers is necessary (50). If manufacturers cannot directly negotiate CT price because of antitrust laws, a third party (e.g., HTA, government agency) could mediate. Third parties allow price adjustments according to the value added and may mitigate tensions between sellers and buyers. Another option for negotiations is applying a safe harbor clause, which eliminates legal or regulatory liability when certain conditions are met; for instance, a PFS target for patients with MM. In this case, negotiations between manufacturers could be allowed if the objective is to adjust the price of the backbone treatment and define the value of the add-on (49).

Payers often implement utilization-management tools, such as prior authorization and step therapy according to CPGs, to ensure appropriate drug use in patients that will benefit the most. Given this restriction, traditional pricing and reimbursement models are a barrier to access. Different pricing and payment models, for instance indication-based pricing, may encourage the development of alternative systems to one based on arbitrary rebates, simple price-volume agreements, and budget caps. Although there is no one-size-fits-all approach to overcoming these challenges, key strategies are outlined below.

Innovative contracting and negotiation strategies
Once CTs pass the HTA process and a value is estimated for each constituent, they are subject to negotiation strategies for setting a purchasing price. Current purchasing frameworks in LA use one of three standard strategies: national/international bidding, restricted invitation for bidding, or direct adjudication. Under these frameworks, prices for most constituents are negotiated and purchased independently as the legal framework limits the use of alternative contracting schemes. However, some LA countries, notably Brazil and Colombia, have recently developed national commissions charged with negotiating entry prices for public purchase. The commissions may be ideal vehicles to gradually adjust the legal framework to systematically use some of the alternative schemes presented below.

Differential pricing (DP)
DP systems can increase access to novel drugs, including high-price constituents of a CT, while leading to increased sales derived from expanding low- and middle-income markets. This approach, currently used in Brazil and Colombia, could also provide opportunities for payers to compete for some indications and as a result, lower their prices. This strategy is used if some CT constituents have competing drugs available; some do not. However, participating in a differential pricing scheme may raise legitimate concerns regarding reliable information about markets, political will from authorities, and commitment from pharmaceutical companies (67).

Indication-based pricing (IBP)
IBP can be applied to drugs with multiple indications that may offer different benefits to different groups of patients (e.g., first line vs advanced disease in MM) since the value of the drug may differ by indication. Under current purchasing frameworks, purchasers request a total volume of the constituent to be used in the different indications to obtain a lower price (68). IBP could be implemented on purchase bases, separating the purchase volumes by indication and establishing a maximum price for each case. This modification will generate a greater administrative burden for the purchaser but will provide long-term benefits by guiding future R&D investment as revenues reflect the incremental value to patients from all indications, and companies will invest in molecules that bring the most value. The underlying economics of IBP should be carefully considered because the same access-expanding pricing flexibility also allows manufacturers to increase prices for high-value indications (69).

Combination-based pricing (CBP)
CBP addresses the challenge that assumes the clinical value of a CT is not simply the sum of the clinical value of the drugs used separately. CBP seeks to resolve the complexities in assigning value and negotiating prices for multi-branded CTs. CBP could be implemented in the purchase bases by listing all the constituents with their respective estimated added values and establishing a maximum CT price that will be weighted by each added value. This modification in the bases will generate a greater administrative burden for the purchaser but could set mid-term precedents in the purchasing system by reducing drug prices for low-value indications and, at the same time, will not increase drug prices for high-value indications.
Managed entry agreements (MEAs)
MEAs are arrangements between producers of the technology and healthcare payers that allow for coverage of new drugs, including CTs, while managing uncertainty around their financial impact or performance in real world settings (7). MEAs help resolve complications of VBP at net price levels only in single-branded CTs where a robust outcome monitoring process can be conducted. In multiple-branded CTs, multilateral arbitration and negotiation between payers and manufacturers theoretically could be used. However, current restrictive antitrust legislations may prohibit these mechanisms (49, 70-71). MEAs can be of two types:

• Outcomes-based payments (OBP), also known as pay-for-performance or risk sharing, describe an approach in which the price paid for the drug is linked to patients’ real-world outcomes considering the patient subtypes with respect to the probability of treatment benefits (72). Although OBP strategies generally focus on clinical outcomes to determine reimbursement, the degree to which OBPs represent the outcomes that are most important to patients can be heterogeneous (73) and has been put forward as a mechanism to accelerate access (74) and mitigate unaffordability (75-76).

• Financial-based payments (FBP), where the price is defined by observable financial performance measured through any of the following indicators: a) price based on manufacturer’s market share; b) price-volume; c) price by channel in which a discount is set on certain products/channels; d) capitation considering a discount for specific patients; e) free initiation with patient/dose dependent discount; f) price discount based on manufacturer’s portfolio; g) subscription payments (51, 76).

In some circumstances, subscription payments may be used to decouple payments from the number of patients that receive the drug. Such a model could help payers anticipate the budget impact associated with treatment for a given disease area, thus ensuring its sustainability. There is a distinct form of lump-sum payments, where a fixed amount is paid for a given volume. The variations of these agreements address different aspects, such as hidden price discounts (e.g., discounts that bypass international referencing practices and which are used in many health systems), uncertainty about the performance of the product in real-world context, and commercial agreements.

From these two types of MEA, payers often prefer FBP as there is no need to collect data in clinical settings, reducing administrative burdens. However, there is evidence that despite the administrative and data collection challenges, manufacturers would be willing to explore the use of OBP (72).

Over-time payments
Also referred to as staggered payments, over-time payments allow payers to pay manufacturers over fixed periods for each patient that receives therapy. This structure may mitigate the high upfront cost otherwise associated with one-off therapies. When the over-time payment is linked to a particular outcome, necessitating the collection of RWD, payers can address uncertainty of the clinical value by the nature of the evidence available at launch (51).

Reassessment of backbone therapy price
Entry price negotiations that address each economy’s particularities is crucial to improving CT access, especially for multi-branded CTs. In these cases, negotiation between manufacturers is necessary to reassess and adjust the price of the backbone therapy to make the CT adequately cost-effective and to determine the price of the add-on therapy. Ideally, this negotiation is proportional to the added value that it produces (77). During this process, negotiators should consider how close the price of the backbone therapy is to the WTP limit.

Improving the Reimbursement Environment
Establishing legal budgetary assessments according to the laws and eligible populations of each country to improve reimbursement policies would avoid the transfer of the budgetary impact to the public and private sectors without the corresponding financial support. Reimbursement should be adjusted based on forecasted GDP changes, national interest rates, exchange rates, and technology approval processes at the local level. Such reimbursement policies prioritize patient outcomes.

Planning and Budget Sustainability
Health policies aimed at the group of super consumers (the small percentage of patients that consume a high amount of the resources allocated to health, as in the case of patients with MM who require high-price treatments for longer time) are needed to allow more balanced health systems that are less likely to be subjected to the excessive stress of underfunding. Overall, these policies should increase transparency, align stakeholder forces, and put population and individual patients at the center of decision-making. Figure 2 presents a situation map for improving access to CTs for MM in LA.

Conclusion
While many challenges exist to improving access to CTs in LA, feasible solutions are on the horizon and urgently needed. Overcoming these barriers will require an orchestrated effort from all stakeholders involved. Value-sharing frameworks adapted to CT that measure added clinical benefit through indicators such as PROs, PFS, OS, MRD, and/or ORR and backbone therapy reassessments are crucial to capture the true value of CT constituents. Innovative pricing and contracting mechanisms such as combination based-pricing, indication-based pricing, and MEAs may be useful to address challenges regarding the combined clinical value of products used in CT, which is not simply the sum of the drugs used separately. Pricing negotiations, especially for multi-branded CT, would benefit from flexibility in competition legislation. In general, structuring a payment model in oncology requires delicately balancing standardization, flexibility, quality, and efficiency.

This panel has addressed issues related to the lack of access to cutting-edge therapies in LA, especially in the context of MM. However, access to cancer innovations is of global interest and the specific issues described are not exclusive to this Region. With increasing healthcare costs and limited resources, there is an opportunity to apply the proposed steps and recommendations to comprehensively address CT access in cancer care. This consensus is not a one-size-fits-all solution and can be tailored to each context on a country-by-country basis.
Papers useful for the consensus discussion and the references cited in this paper were identified through searches of PubMed and Embase with the search terms “multiple myeloma”, “combination therapy”, “drug pricing in Latin America”, and “combination therapy for multiple myeloma in Latin America” from 2014 until 2021. Articles were also identified through the bibliographies of the papers identified in the search as well as from searches of the authors’ own files. Particular attention was paid to papers that reviewed or summarized the topic in question or were related to activities in LA. The final reference list was generated based on the relevance to the scope of this manuscript.

Table 1. Overview of Argentina, Brazil, Colombia and Mexico’s HTA, Regulatory, Pricing and Reimbursement Landscape.

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>POPULATION (MILLIONS)</th>
<th>HEALTH EXPENDITURES* (% of GDP)</th>
<th>HTA AGENCY</th>
<th>REGULATORY AGENCY</th>
<th>PRICING</th>
<th>REIMBURSEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>45.37</td>
<td>9.62</td>
<td>CONETEC</td>
<td>ANMAT</td>
<td>No universal pricing policy. Published in Karios and Manual Farmacéuticos Argentinos. HMOs negotiate discounts.</td>
<td>Drugs included in PPO (Mandatory Medical Plan) are reimbursed. Drugs reimbursed outside PPO varies by HMOs. (Only bone marrow and lenalidomide are included in PPO)</td>
</tr>
<tr>
<td>Brazil</td>
<td>212.55</td>
<td>9.51</td>
<td>CONETEC</td>
<td>ANVISA</td>
<td>CMED</td>
<td>Drugs included in RENAME or RN by the MoH are reimbursed by the SUS. Rol de procedimientos es eventuamente es determinado por ANS (Private System).</td>
</tr>
<tr>
<td>Colombia</td>
<td>50.88</td>
<td>7.64</td>
<td>IETS</td>
<td>INVIMA</td>
<td>National Commission for the Prices of Medicines and Medical Devices - CNPMMD</td>
<td>Drugs included in PBS (Basic Health Plan) by the MoH are reimbursed. The non-PBS must be justified by physicians or legal action can be taken.</td>
</tr>
</tbody>
</table>


Box 2. Standard of Care Therapy for MM

- First-line Patients/transplant-eligible:
  - Induction: Bortezomib + Lenalidomide, thalidomide, or cyclophosphamide + dexamethasone +/- daratumumab
  - Transplant: High dose melphalan + ASCT
  - Maintenance: Lenalidomide

- Transplant- ineligible CT Options:
  - Bortezomib + cyclophosphamide + dexamethasone
  - Bortezomib + lenalidomide + dexamethasone
  - Bortezomib + melphalan + prednisone
  - Daratumumab + bortezomib + melphalan + prednisone
  - Daratumumab + lenalidomide + dexamethasone
  - Lenalidomide and dexamethasone

- Relapse Patients:
  - Treatment must be individualized using combinations with three or two of the following drugs (Triplet CT preferred):
    - Bortezomib
    - Ixabepilone
    - Carfilzomib
    - Ixazomib
    - Daratumumab
    - Lenalidomide
    - Dexamethasone
    - Pomalidomide
    - Elotuzumab
    - Thalidomide
    - Prednisone
    - Melphalan
    - Cyclophosphamide

ASCT may be an option in the relapsed setting for fit patients not undergoing ASCT in first line or those with a long duration of response after upfront ASCT.

Table 2. Access to CTs for MM in the Public and Private Sectors in Argentina, Brazil, Colombia and Mexico, with discrepancies highlighted

<table>
<thead>
<tr>
<th>CT</th>
<th>ARGENTINA</th>
<th>BRAZIL</th>
<th>COLOMBIA</th>
<th>MEXICO</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>Public</td>
<td>Private</td>
<td>Public</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(Contributive branch of “Public System”)</td>
<td></td>
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<tr>
<td>FIRST-LINE THERAPY ELIGIBLE</td>
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<tr>
<td>Dara-VTD (36)</td>
<td>Approved</td>
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<td>VRD (37)</td>
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<tr>
<td>Transplant</td>
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<td>Isa+Pd</td>
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Notes: Legend: green = good access; yellow = limited access; red = very limited or no access; *= off-label use; Dara- VTD = daratumumab + bortezomib + thalidomide + dexamethasone; VRd = bortezomib + lenalidomide + dexamethasone; VTD = bortezomib + thalidomide + dexamethasone; VCD = bortezomib + cyclophosphamide + dexamethasone; Dara-VMP= daratumumab + bortezomib + melphalan + prednisone; Dara-RD = daratumumab + lenalidomide + dexamethasone; VMP = bortezomib + melphalan + prednisone; RD= lenalidomide + dexamethasone; Dara-VD= daratumumab + bortezomib + dexamethasone; Dara -KD = daratumumab + carfilzomib + dexamethasone; Carfil-RD = carfilzomib + lenalidomide + dexamethasone; Isa-RD = izzoxomib + lenalidomide + dexamethasone; Elo-RD = elotuzumab + lenalidomide + dexamethasone; Pom-VD = pomalidomide + bortezomib + dexamethasone; Dara -PD = daratumumab + pomalidomide + dexamethasone; Carfil-Dex = carfilzomib + dexamethasone; Pd = Pomalidomide + dexamethasone. The text in the table represents where conflicting approval and access scenarios exist.
Box 3. Types of CTs

- **Novel + Novel**: combination of two new products
- **Novel + Existing**: combination of a new product and a product that is already approved
- **Existing + Existing**: combination of two products already approved separately
- **Existing combination**: combination of two products already approved as a combination for a given indication.

Box 4. Recommended indicators for Multicriteria Health Value Analyses applied to CT

1. PROs
2. Baseline DALYs and DALYs averted
3. Cost per DALY averted
4. Baseline QALY and QALYs gained
5. Cost per QALY gained
6. Incremental cost of the therapies
7. Incremental effectiveness of the different therapies
8. Organizational impact of the introduction of CT
9. Analysis of the implementation process to achieve the desired impact
10. Measurement of net health benefit and cost per month
11. Life years gained (LYG)
12. Cost per respondent
13. Number needed to treat (NNT)

Notes: Legend: PROs: Patient Reported Outcomes. DALY: disability-adjusted life years. QALY: quality adjusted life years. CT: combination therapies. For further details on PROs, DALYs and QALYs refer to appendix 1.

Figure 1. Alternate HTA framework for Combination Therapies (64)

Notes: Legend: DALY: disability-adjusted life years; QALY: quality-adjusted life years; CT: combination therapies; MM: multiple myeloma; HTA: health technology assessment; CAVALA: cancer value label. For further details on the CAVALA framework refer to appendix 2.
Appendix 1

PROs in the CT context
While there is no international consensus about a PRO framework for oncology there are some guidelines from official agencies such as the FDA (78) that mention a core set of PROs that can become relevant in the context of clinical trials for anti-cancer therapies intended to demonstrate an effect on survival, tumor response or delay in the progression of a malignancy as in the case of CT. The core set of PROs include:

- Disease-related symptoms
- Symptomatic adverse events
- Overall side effect impact summary measure
- Physical function
- Role function

It is best practice that the selection of the instrument to measure the core PROs be fit-for-purpose, meaning that it is appropriated for its intended use, its measures on concepts that are clinically relevant and important to patients are valid and reliable, and data can be communicated accurately, interpretably, and it is not misleading.

Cost calculation per DALY averted by CT
a. Obtain information on prevalence, incidence, lethality, clinical disease course, main disease involvements, and disability weights for each measured outcome.
b. Create a Markov model, wherein the disease can be modeled according to clinical course per the national life expectancy. Then measure DALYs without treatment(s) and with treatment(s).
c. Compare the DALYs obtained with global data, measuring this outcome in different diseases.
d. Review DALY changes achieved throughout the clinical course with the incorporation of CT. Define the number of subjects who require such treatments and the alternatives. This information may generate a new DALY averted measure per each CT.
e. Measure all DALYs averted per CT in terms of costs in order to understand the substantial investment required to produce the treatments (costs of CT). These measurements generate information on DALYs earned per CT and incremental therapy costs.

Cost calculation per QALY gained by CT
A methodology internationally accepted for QALY calculation follows the Euroqol framework:
1. An EQ-5D-5L value set should be developed for the country.
2. The EQ-5D-5L questionnaire and value set are used all along the time the clinical trial for each CT lasts. The measurement before the clinical trial starts will provide the data for the baseline QALY.
3. Calculate the average QALYs gained based upon the data from the clinical trial.
4. The average QALY gained will divide the present value of the total cost of the CT considering the average duration on treatment.

Appendix 2

While there are several frameworks developed to measure the value of oncology treatments, (notably ESMO, ASCO, ICER frameworks), these remain weak on the homogeneity of the measurement, generating reasonable doubts about different treatments being valued differently. This weakness is particularly relevant when measuring value generated by CT (79).
The Cancer Value Label (CAVALA) framework was developed by the Portuguese Institute of Oncology (IPO-Porto) as an alternative to assess the degree of innovation in oncology technologies, including CT. The basic assumption used is that the value of a treatment is measured by the relationship between its results and the amounts of resources it requires. To operationalize this assumption, a decision matrix is developed (Figure A). The CAVALA methodology allows the use of a series of indicators of expected results that include the years of life gained, quality of life, progression-free survival, average survival, among others.

This flexibility generates a multidimensional decision matrix in which there is an expected cost axis and as many axes as health outcomes are being analyzed on the same set of comparable health technologies. These parameters are categorized in four possible levels of answer. The result of the analysis consistently categorizes the technologies in one of four innovation outcomes. The matrix categorization is particularly useful for CT as it allows to measure the added-value from the backbone, from the add-on component and of the CT as overall.

Appendix 1 Figure A. CAVALA decision matrix (the example of only one expected outcome is presented).

<table>
<thead>
<tr>
<th>Expected costs (difference between total cost of treatment in comparison to baseline treatment or other treatments)</th>
<th>Expected outcomes (difference in life years, quality of life, other valid outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A ≤ 25%</td>
<td>A ≥ 75%</td>
</tr>
<tr>
<td>B [25%, 50%]</td>
<td>Added-value innovation</td>
</tr>
<tr>
<td>C [50%, 75%]</td>
<td>No added-value as the cost of the innovation is disproportionate respect to expected outcomes</td>
</tr>
<tr>
<td>D ≥ 75%</td>
<td>Not-innovative technology</td>
</tr>
</tbody>
</table>

The CAVALA methodology provides information that allows to support decisions on prices and on establishing criteria for the inclusion of health technologies in the positive purchase or reimbursement lists of health systems, considering a robust two-dimensional perspective. The method recognizes the full clinical value of a healthcare technology classified as not valuable due to excessive price, giving the opportunity for the manufacturer of the technology to adjust its price in proportion to the health outcomes being measured. It is expected that the full recognition of the clinical value will allow the backbone therapy, the add-on component, and the CT as a whole to be given their proper dimension, identifying which component should be used to establish a price reduction strategy (79).

References


59. Kossukhina MA, Fomin VI. Innovation project value assessment methodology for high-tech enterprises. SHS Web Conf. 201; 35: 01086. doi: 10.1051/shsconf/20173501086


