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Cost-Effectiveness of Bortezomib Plus Cyclophosphamide Plus Dexamethasone Versus Bortezomib Plus Thalidomide Plus Dexamethasone Versus Lenalidomide Plus Dexamethasone as Induction Therapy for Transplant-Eligible Patients with Newly-Diagnosed Multiple Myeloma in Colombia

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Abstract

Objective: To conduct a cost-effectiveness assessment of bortezomib plus cyclophosphamide plus dexamethasone (CyBorD) versus bortezomib plus thalidomide plus dexamethasone (VTD) versus lenalidomide plus dexamethasone (RD) as initial treatment for transplant-eligible patients with newly-diagnosed multiple myeloma (MM), from a Colombian payer perspective.

Methods: A Markov model was developed to estimate quality-adjusted life years (QALYs), direct costs and incremental costs per QALY gained associated with use of three chemotherapy regimens over a patient's lifetime. Information on the efficacy, security and costs of the regimens was based on data from phase III clinical trials and national tariff respectively. Direct costs included the costs of CyBorD, VTD and RD, treatment of adverse events, prophylaxis and monitoring associated with MM. Post-progression direct costs included costs of bortezomib plus lenalidomide plus dexamethasone and monitoring for progressive disease. Utilities were obtained from the published studies and Tufts registry. Costs and outcomes were discounted at 0%, 3.5%, 5%, 7% and 12% annually. A probabilistic sensitivity analysis (PSA) using Monte Carlo simulation was performed.

Results: The undiscounted costs of CyBorD, RD and VTD were USD $48.892; $50.863 and $52.835 respectively. QALY´s for these alternatives were 5.53, 3.48 and 4.03 respectively (undiscounted). RD and VTD were dominated by CyBorD. This finding was robust in the PSA for each iteration.

Conclusion: CyBorD dominated to VTD and RD as induction therapy of chemotherapy in transplant-eligible patients with active MM and standard risk from the Colombian payer perspective.

Keywords: Cyclophosphamide; Bortezomib; Dexamethasone; Thalidomide

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Introduction

Multiple myeloma (MM) is a malignant neoplasm characterized by the proliferation of plasma cells causing monoclonal immunoglobulins favoring the presence of infections, anemia, bleeding, bone lesions and increase in blood viscosity. This condition represents approximately 1% of the neoplasic diseases in general with an annual incidence of 35 cases per 100,000 persons- year in people between 75 and 79 years mainly affecting patients in the sixth decade of life. The survival at 5 years is currently 34% [1,2].

New therapies have contributed to the improvement in survival. The recommended therapy for this condition is the autologous stem cell transplant (SCT) previous administration of chemotherapy. The purpose of chemotherapy is to reduce the tumor burden to promote the mobilization of hematopoietic progenitors. However the high risk of myelotoxicity by some agents has generated concern about its safety. The safety profile of the new drugs such as bortezomib and lenalidomide has led to their increasing use as induction and maintenance therapy in patients with this condition.

The effectiveness of these new agents has been demonstrated in recent systematic reviews. According to these studies, patients with MM who receive schemes that include bortezomib or lenalidomide are more likely to have complete response, very good partial response, overall survival and progression free survival compared to those who did not receive schemes with any of these agents [3-6]. Therefore, several clinical practice guidelines, including the National Comprehensive Cancer Network (NCCN) and the Mayo Clinic guidelines include them as drugs of first choice in patients candidates to SCT in combinations with other agents [7,8].

In spite of its clinical effectiveness the main disadvantage of these drugs is the high cost. Although there are several published economic evaluations, these have been carried out in developed countries mainly [9,10]. In addition, a large proportion of the studies included patients who have received chemotherapy or transplantation previously and are in relapse of their disease. Based on the foregoing, the implementation of a thorough economic evaluation in the Latin American context would provide data that will allow the decision-maker to include or not these medications in the plan of benefits of the health system for patients without previous chemotherapy or transplantation. In effect, this evaluation in particular was carried out with the purpose of evaluating the efficiency of bortezomib and lenalidomide to decide on their inclusion in the public benefits plan with this indication in Colombia.

The objective of the present study is to quantify the incremental cost-utility ratio (ICUR) of the regimen of bortezomib plus cyclophosphamide plus dexamethasone (CyBorD) versus bortezomib plus thalidomide plus dexamethasone (EDV) versus lenalidomide plus dexamethasone (RD), in patients with active MM and standard risk candidates to SCT in Colombia.

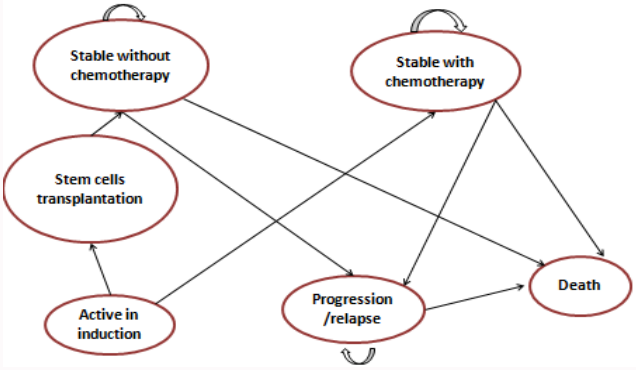

Figure 1: Structure of the Markov model.
The Markov model consists of the following states: (A) active in induction: patient with diagnosis of multiple myeloma (MM) with standard risk receives four cycles of any chemotherapy regimen. The event that allows the entrance to this state is the diagnosis of MM eligible to stem cell transplantation (SCT). The event that allows the output of this state is the decision of the physician and the patient to perform SCT or continue with chemotherapy only taking into consideration the initial response to it. (B): Stem cells transplantation: This temporary state represents the patient who has chosen this procedure. (C) Stable with chemotherapy: The patient who has received four cycles of chemotherapy continues receiving, by personal decision or medical recommendation, cycles of this regimen until the progression or remission of the condition. The event that allows the transition toward the state of progression is the clinical or laboratory evidence of progression of the disease according to NCCN criteria. (D) Stable without chemotherapy: In this state, the patient who underwent four cycles of chemotherapy and SCT, receive bortezomib for 24 months or until the progression or remission of the condition. The event that allows the transition toward the state of progression is the clinical or laboratory evidence of progression of the disease according to NCCN criteria. (E) Progression/relapse: In this state the patients presents clinical criteria of progression or recurrence of their condition. The patients in this state receive bortezomib-lenalidomide and dexamethasone regimen. The event that allows the transition is MM related death.

Methodology

A cost utility analysis with a decision model was conducted from the Colombian Health system's payer perspective. The target population included patients older than 18 years with diagnosis of active MM with standard risk candidates to SCT treated in third-level hospitals and who have not received chemotherapy or transplantation previously. It was considered patients at standard risk because it represents the largest proportion (60%) of the patients with MM [7]. Ideally there should be an analysis by subgroup according to the cytogenetic profile; however the absence of data in the published studies did not allow it.

The alternatives evaluated were three regimen of induction chemotherapy prior to the SCT. The first regimen is CyBorD: it consists of 4 cycles of 28 days of bortezomib in doses of 1.3 mg/m^2 subcutaneous the days 1, 4, 8 and 11; plus cyclophosphamide 500 mg intravenous the days 1, 8, 15 and 22, plus dexamethasone 40 mg intravenously the days 1, 8, 15 and 22. The second regimen is VTD and consists of 4 cycles of 28 days of bortezomib in doses of 1.3 mg/m^2 subcutaneous the days 1, 4, 8 and 11; plus thalidomide of 200 mg orally every day plus dexamethasone 40 mg intravenously the days 1,

Table 1: Survival function for calculating transition probabilities in the model.

	Survival function used to calculate transition probabilities from stable with chemotherapy to progression		Ref
	Time (months)	Survival function	
CyBorD	0≤t≤11	1	12
	11<t≤31	$e^{-0.02202062*(t-11)}$	
VTD	0≤t≤56	$e^{-0.01582305*t}$	13
RD	0≤t≤41	$e^{-0.02618681*t}$	14
	Survival function used to calculate transition probabilities from progression to death		
	Time (months)	Survival function	
CyBorD	0≤t≤25	1	12
	25<t≤28	0.88	
VTD	0≤t≤56	$e^{-0.00569536*t}$	13
RD	0≤t≤25	$e^{-0.0055188*t}$	14
	25<t≤42	$e^{-(0.01636128*(t-25))-0.12}$	

Table 2: Model parameters.

Model parameters		Range		References
COSTS (USD)	Base case	Minimum	Maximum	
Cost per cycle CyBorD				
Bortezomib	2.951	2.950	3.257	
Ciclofosfamide	22	18	27	
Dexametasone	0.5	0.4	0.9	
Chemotherapyrooms	21	21	21	
Prophylactic – adjuvantmedication	155	135	163	
Diagnostictests	446	446	446	
Total cost per cycle CyBorD without adverse drugs reactions	3.596	3.570	3.914	
Cost per cycle VTD				
Bortezomib	2.951	2.950	3.257	
Ciclofosfamide	22	18	27	
Dexametasone	0.5	0.4	0.9	
Chemotherapyrooms	11	11	11	
Prophylactic – adjuvantmedication	155	135	163	
Diagnostictests	446	446	446	
Total cost per cycle VTD without adverse drugs reactions	3.585	3.560	3.904	
Cost per cycle RD				
Lenalidomide	4.220	4.021	4.420	
Dexametasone	1.5	1.48	2.7	
Chemotherapy rooms	11	11	11	National tariff ISS, Minister of Health´s circular, SISMED
Diagnostic tests	446	446	446	
Total cost per cycle RD without adverse drugs reaction	4.679	4.479	4.880	
Cost of stem cells transplantation	39.576	31.988	47.164	
Cost of maintenance therapy				
Bortezomib	1.476	1.474	1.628	
Chemotherapy rooms	5	5	5	
Prophylactic medications	37	33	38	
Diagnostic tests	73	73	73	
Total cost of maintenance therapy per month	1.591	1.585	1.744	
Treatment of adverse drugs reaction				
Zoster herpes	8.2	5.7	9	
Deep venous thrombosis	34.5	30.5	69.3	
COST PER MARKOV STAGE				
Cost active CyBorD	3.706	3.573	3.916	
Cost active VTD	3.735	3.695	4.062	
Cost active RD	4.479	4.487	4.898	
Cost stable for all alternatives	1.590	1.586	1.745	
Cost progression for all alternatives	6.990	6.989	7.696	
UTILITIES FOR MARKOV STAGES				
Utility active CyBorD	0.636	0.611	0.81	
Utility stable without chemotherapy CyBorD	0.69	0.46	0.8	
Utility stable with chemotherapy CyBorD	0.665	0.626	0.8	
Utility progression CyBorD	0.636	0.485	0.64	16-19
Utility active with induction VTD	0.636	0.611	0.81	
Utility stable without chemotherapy VTD	0.69	0.46	0.8	
Utility stable with chemotherapy VTD	0.665	0.626	0.8	
Utility progression VTD	0.636	0.485	0.64	
Utility active with induction RD	0.566	0.5	0.81	16-20
Utilit stable without chemotherapy RD	0.69	0.46	0.8	16-19
Utility stable with chemotherapy RD	0.604	0.5	0.8	16-20
Utility progression RD	0.566	0.485	0.64	

Table 3: The probability distributions and their parameters.

Parameter	Type of distribution	Parameters of the distribution		Reference
		Minimum	Maximum	
Utility active CyBorD	Uniform	0.611	0.81	17-19
Utility active RD	Uniform	0.5	0.81	16.18,19
Utility active VTD	Uniform	0.611	0.81	17-19
Utility stable without chemotherapy for all alternatives	Uniform	0.46	0.8	17-19
Utility stable with chemotherapy	Uniform	0.626	0.8	17-19
Utility stable with chemotherapy RD	Uniform	0.5	0.8	16,18,19
Utility stable with chemotherapy VTD	Uniform	0.626	0.8	17-19
Utility progression CyBorD	Uniform	0.485	0.64	17-19
Utility progression RD	Uniform	0.485	0.64	16,18,19
Utility progression VTD	Uniform	0.485	0.64	17-19
Costs active CyBorD	Uniform	3.572	3.915	National Tariff ISS
Costs active RD	Uniform	4.487	4.898	
Costs active VTD	Uniform	3.695	4.061	
Costs progression all alternatives	Uniform	6.988	7.696	
Costs stable all alternatives	Uniform	1.586	1.744	

8, 15 and 22. The last regimen is RD and consists of 4 cycles of 28 days of oral chemotherapy of lenalidomide 25 mg the days 1 to 21 plus intravenous dexamethasone 40 mg the days 1-4, 9-12 and 17-20. These regimens were chosen because they represent the most used schemes in Colombia as reported by experts consulted and are recommended as first-line regimens for the clinical practice guidelines of the NCCN and Mayo Clinic [7,8].

The time horizon was 20 years with an annual discount rate for costs and outcomes in health of 5% for the base case. A sensitivity analysis was performed with rates of 0%, 3.5%, 7% and 12% according to the rates recommended by the Colombian methodological manual [11]. This time horizon was chosen because the greatest proportion of patients is diagnosed in the sixth decade of life so that a period of 20 years detects the costs and outcomes across the life expectancy.

It was considered to perform the assessment using a Markov model because the MM is a chronic condition with recurrent health states throughout its natural history. For this an exhaustive search of literature was conducted in order to find previous models with the structure that will adjust to the target population. Because they were not found, a Markov model *de novo* was built and it was evaluated using a hypothetical cohort. The structure of the model was validated with clinical experts in Colombia and is presented in figure 1.

The assumptions of the model are:

1. All patients received four cycles of chemotherapy before deciding the transplantation. This is based on clinical trials in which the SCT or continue chemotherapy is defined in this time [12-14].

2. There is no death by MM in the first four cycles [12-14].

3. The "Stable with chemotherapy" and "Stable without chemotherapy" states were separated in order to consider patients who by medical recommendation or by personal choice had decided to continue with chemotherapy and not be subjected to SCT once completed the fourth cycle of induction. This is justified in that, despite that the SCT is the first alternative in the treatment of this condition, less than 30% of patients decide for this procedure [12-14].

4. The patients "Stable with chemotherapy" or "Stable without chemotherapy" states might die without passing through the "Progression/Relapse" state. It has been reported that approximately 30% of the patients died without progression [14].

5. The patients in "Progression/Relapse" state are treated with a regimen of bortezomib, lenalidomide and dexamethasone in Colombia. This option was validated by clinical experts.

6. It was assumed that in the schema VTD the transition probabilities of the "Stable with chemotherapy" state to "Progression/Relapse" or "death by MM" states were the same as those of the group of CyBorD. This is based on the fact that the PETHEMA/GEM trial did not disaggregated these probabilities in patients with SCT, of those who did not receive SCT, since the latter were excluded from the study [13].

The Markov cycles of one month throughout the time horizon was chosen, i.e. 240 cycles with half-cycle correction. The transition probabilities from "Active" to "Stable with chemotherapy" or "Stable without chemotherapy" states were obtained directly from the studies [12-14]. The transition probabilities from "Stable with chemotherapy" or "Stable without chemotherapy" to "Death by MM", i.e. the death without progression or relapse, were calculated on the basis of the cumulative incidence of the same studies. In this case the mortality rate was calculated and then the probabilities were recalculated. The transition probabilities for each cycle were obtained from the curves of progression-free survival or overall survival of controlled clinical studies [12-15]. The table 1 shows the functions of survival obtained of these curves.

The outcome measure used was the QALY. This measure was chosen because the MM affects the health-related quality of life. The Kaplan Meier curves in EVOLUTION, PETHEMA/GEM phase III and Rajkumar studies were used in order to calculate the life-years for CyBorD, VTD and RD respectively [12-14]. These were chosen because they are good quality studies included in several systematic reviews and they include the alternatives. Because of the time horizon of this evaluation is longer than the follow-up period of clinical

Table 4: Deterministic incremental analysis of evaluated chemotherapy regimens for multiple myeloma.

Including all alternatives with a discount rate of 0%					
Alternatives	Cost USD	Incremental cost	QALY	Incremental QALY	Incremental cost utility ratio
CyBorD	48.892		5.53	-	-
RD	50.863	1.971	3.48	-2.05	Dominated
VTD	52.835	1.972	4.03	0.55	Dominated

Table 5: Results of probabilistic sensitivity analysis using second order Monte Carlo simulation.

	Costs				QALY			
	Minimum	Mean	Maximum	Standard deviation	Minimum	Mean	Maximum	Standard deviation
CyBorD	46.593	48.904	51.177	885	5.07	5.53	6.0	0.16
VTD	50.266	52.844	55.419	1.033	3.4	4.02	4.7	0.25
RD	48.455	50.873	53.254	849	2.8	3.48	4.1	0.23

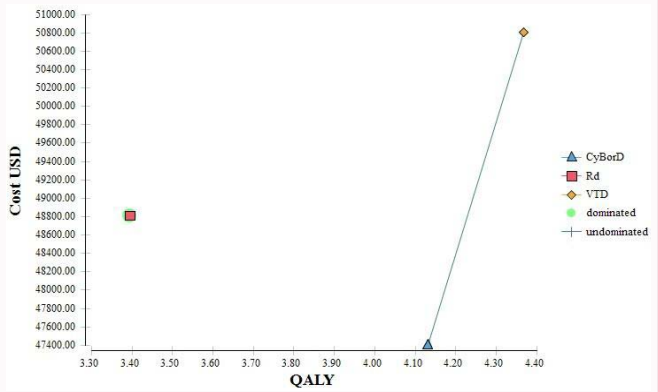

Figure 2: Cost effectiveness plane of the alternatives in multiple myeloma.

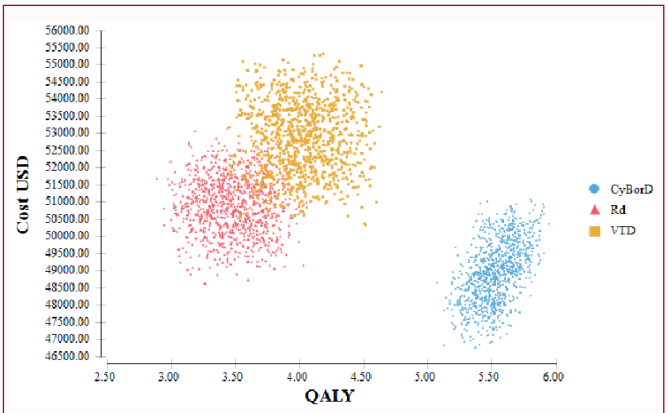

Figure 3: Probabilistic sensitivity analysis of the alternatives in multiple myeloma.

trials, the most suited survival function for each alternative was determined and subsequently was extrapolated using the last hazard rate assuming a decreasing Weibull function. The values of Markov states were obtained from clinical studies that evaluated utilities using the EQ-5D and the values in the Center for the Evaluation of Value and Risk in Health of the Tufts Medical Center [16-20]. The table 2 shows the utilities values for each Markov states.

The NCCN guideline, clinical trials and the expert opinion were utilized in order to identify and measure the resources invested in these patients. For each scheme of chemotherapy, the resources utilized in induction phase, adjunctive therapy, prophylaxis and management of adverse reactions to medicines grade 3 or 4 and monitoring were calculated. The evaluation of the medications, procedures and laboratory tests was based on national tariff (SISMED and regulatory resolutions of Ministry of Health for medications and ISS tariff for procedures and diagnostic test). The value of the inputs was gathered from third-level medical centers in three main cities of Colombia. The costs were expressed in US dollars using an exchange rate of 1 USD=COP 3,000 corresponding to the mean value in November 2015. The willingness to pay threshold was USD 23.790 corresponding to 3 times the gross domestic product (GDP) per capita in Colombia in 2015 [21].

A probabilistic sensitivity analysis was executed using a second order Monte Carlo simulation with 10,000 iterations using software Tree Age 2013. The probability distributions and their parameters are expose in the table 3.

Results

The table 4 presents the deterministic incremental analysis for each alternative. The alternative CyBorD dominated the other alternatives. The costs of CyBorD at discount rates of 3.5%, 5%, 7% and 12% were USD 24.571, 18.426; 12.634 and 5.068 respectively. The discounted QALY´s at these rates were 2.78; 2.08; 1.42 and 0.57 respectively. The table 5 presents the results of the probabilistic sensitivity analysis using second order Monte Carlo simulation. The figure 2 represents the scatter plot for the different alternatives in the cost-effectiveness plane showing that the alternative CyBorD is more efficient in comparison to the other two alternatives. The figure 3 represents the incremental cost effectiveness plane. The total of iterations was localized in the southeast quadrant. The figure 4 shows the acceptability curve. This figure reveals the total iterations of CyBorD were cost effective for the willingness to pay.

Discussion

The CyBorD regimen for patients with active MM with standard risk dominated to VTD and RD regimens, from the perspective of the payer in the public health system of Colombia for willingness to pay between 1 to 3 times the GDP per capita.

The comparison of these findings with other evaluations is limited due to the absence of studies that compare the same alternatives, different models structures and the type of model. Nevertheless, the results of this economic evaluation are according to general trends identified in other studies. Firstly, the three-drug regimens tend to have greater efficiency than two-medication regimen. Secondly, the inclusion of the new medications (e.g. bortezomib) increases the cost significantly. However, this raise in costs is below the willingness to

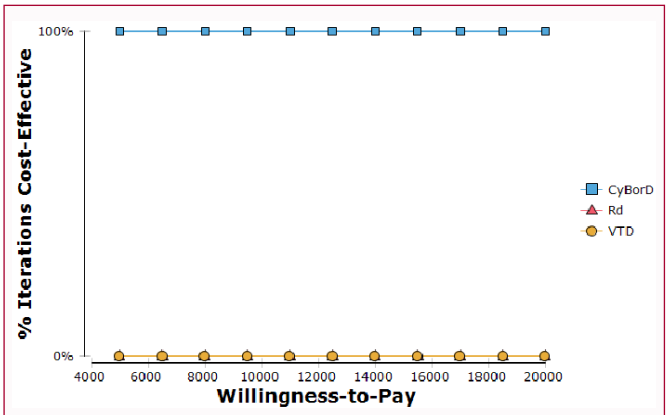

Figure 4: Acceptability curve of the alternatives in multiple myeloma.

pay threshold in several systems of health. Garrison *et al.* [9] concluded that the three- medications schema, i.e. bortezomib plus melphalan plus prednisolona, provided better health outcomes at lower cost compared tomelphalan plus prednisolona only, melphalan plus prednisolone plus thalidomide or lenalidomide plus melphalan and maintenance with lenalidomide in the United States. A NICE report considered the addition of bortezomib to two-medication regimen as a cost-effective alternative in British health system with ICER beneath £30,000 per QALY [22]. Similarly, this agency recognized the multiple constraints in costs, parameters and structure of the model in this assessment [23]. Picot *et al.* [10] also demonstrated the addition of bortezomib to melphalan and prednisolone had a ICER of £29.102 per QALY representing an cost-effective alternative. Other reports also mentioned the addition of bortezomib to two-medication schemes as a cost-effective alternative in the United States and Sweden in patients with active MM [24,25].

With regard to the lenalidomide plus dexamethasone, albeit there are studies on its clinical effectiveness, the data available on the efficiency as first-line therapy are limited. Some studies demonstrated the efficiency in maintenance therapy but there is limited evidence in patients without transplantation [26,27].

This economic evaluation has several limitations. Firstly, the study population is homogenous. The growing evidence about the importance in the determination of the risk through cytogenetic studies and therefore the type of chemotherapy would lead to the quantification of ICER for subgroup of patients according to their risk. Secondly, there is absence of literature related to utilities in the Latin American context in patients with this disorder. Although utility values from other regional studies were considered, mostly US and Europe, these values do not necessarily reflect the Latin-American patients´ preferences. Thirdly, the survival curves are provided from randomized clinical trials with short follow-up periods which contrast with the chronic nature of the entity. In addition to the above, the primary outcome of the most of the studies is the proportion of total or partial response and they did not follow-up the patients who had decided the SCT. In addition, many of these utilities values are not specific to the evaluated alternatives in this assessment but those correspond to other chemotherapy regimens, many of which include melphalan with which has a well-known risk of mielotoxicity.

With regard to the generalization of the results, the following considerations could be taken account. First of all, these results do not necessarily reflect the efficiency of the alternatives in patients with different cytogenetic or molecular profiles. Secondly, although many of the cost data were obtained from national tariffs, the constrained availability of specialists or tertiary medical centers could generate distortions that would produce different ICER.

Although the study did not assess explicitly ethical or equity issues, there are well recognized barriers to access and potential catastrophic risk for the patients. A study in Canada, 81% of the doctors were dissatisfied or very dissatisfied with the access to thalidomide in patients with MM. The reasons for dissatisfaction came from the high cost, the violation of the privacy of the patient and the continuous changes to the chemotherapy regimen because of the lack of access to these [28]. Another study showed that those patients who live in rural areas may have greater difficulties in the treatment of the condition because of the isolation produced by its geographical conditions and the treatment effects [29]. On the other hand, being a chronic neoplasm with the highest prevalence in patients who are not generally in the productive age group is feasible that the condition and its treatment can have catastrophic effects for out-of-pocket expenses. A recent study found that the aspects related with unemployment, disability, health insurance, retirement and out-of-pocket expenses represent the most worrying aspects for these patients. Out of pocket costs represent between 28-36% of incomes, but these might represent 38% in patients receiving chemotherapy [30]. Although it is difficult to generalize the effects on access to health services on the basis of these results, it is feasible to assume that these behaviors can occur in patients in the Latin American context.

In conclusion, the results of this assessment suggest that the CyBorD is dominant compared with VTD and RD as induction therapy of chemotherapy in patients with active MM with standard risk from the perspective of the payer in Colombia.

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