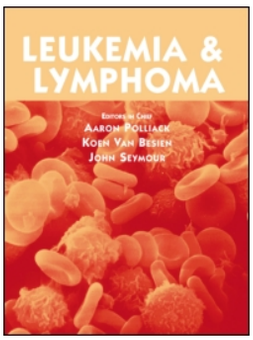

Leukemia & Lymphoma

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

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To cite this article: Camila Peña , Eloisa Riva , Natalia Schutz , Luz Tarín-Arzaga , Humberto Martínez-Cordero , Virginia Bove , Rocío Osorio , Mauricio Chandía , Cecilia Beltrán , Javier Schulz , Daniela Cardemil , Carolina Contreras , Carmen Gloria Vergara , Javiera Donoso , Marcela Espinoza , Gabriel La Rocca , Hernán López-Vidal , Pilar León , Christine Rojas Hopkins , Pablo Soto , Sandra Aranda , Vivianne Torres , Macarena Roa , Paola Ochoa , Patricio Jose Duarte , Guillermina Remaggi , Sebastián Yantorno , Ariel Corzo , Soledad Zabaljauregui , Claudia Shanley , Sergio Lopresti , Sergio Orlando , Verónica Verri , Luis Quiroga , Carlos García , Vanesa Fernández , Jhoanna Ramirez , Alicia Molina , María Pacheco , Alex Mite , Inés Reyes , Brenner Sabando , Francisca Ramírez , Claudia Sossa , Virginia Abello , Henry Idrobo , Kenny Mauricio Galvez Cardenas , Domingo Saavedra , Guillermo Quintero , Raimundo Gazitúa , Lina Gaviria , Rigoberto Gomez , Mónica Osuna , Alicia Henao-Uribe , Omar Cantú-Martínez , David Gómez-Almaguer , Yarely Itzayana García-Navarrete , Antonio Cruz-Mora , Yahveth Cantero-Fortiz , Guillermo J Ruiz-Argüelles & Dorotea Fantl (2020): Different outcomes for transplant-eligible newly diagnosed multiple myeloma patients in Latin America according to the public versus private management: a GELAMM study, Leukemia & Lymphoma, DOI: 10.1080/10428194.2020.1804558

To link to this article: https://doi.org/10.1080/10428194.2020.1804558

Published online: 26 Aug 2020.

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2020.1804558

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ORIGINAL ARTICLE

Different outcomes for transplant-eligible newly diagnosed multiple myeloma patients in Latin America according to the public versus private management: a GELAMM study

Camila Peña[a], Eloisa Riva[b]*, Natalia Schutz[c]*, Luz Tarín-Arzaga[d], Humberto Martínez-Cordero[e], Virginia Bove[f], Rocío Osorio[g], Mauricio Chandía[h], Cecilia Beltrán[i], Javier Schulz[i], Daniela Cardemil[j], Carolina Contreras[k], Carmen Gloria Vergara[k], Javiera Donoso[l], Marcela Espinoza[m], Gabriel La Rocca[n], Hernán López-Vidal[o], Pilar León[p], Christine Rojas Hopkins[q], Pablo Soto[r], Sandra Aranda[s], Vivianne Torres[t], Macarena Roa[a], Paola Ochoa[u], Patricio Jose Duarte[v], Guillermina Remaggi[w], Sebastián Yantorno[x], Ariel Corzo[y], Soledad Zabaljauregui[z], Claudia Shanley[aa], Sergio Lopresti[ab], Sergio Orlando[ac], Verónica Verri[ad], Luis Quiroga[ae], Carlos García[af], Vanesa Fernández[ag], Jhoanna Ramirez[ah], Alicia Molina[ai], María Pacheco[ai], Alex Mite[ai], Inés Reyes[aj], Brenner Sabando[ak], Francisca Ramírez[ak], Claudia Sossa[al], Virginia Abello[am], Henry Idrobo[an], Kenny Mauricio Galvez Cardenas[ao], Domingo Saavedra[ap], Guillermo Quintero[aq], Raimundo Gazitúa[ar], Lina Gaviria[as], Rigoberto Gomez[at], Mónica Osuna[au], Alicia Henao-Uribe[av], Omar Cantú-Martínez[d], David Gómez-Almaguer[d], Yarely Itzayana García-Navarrete[aw,ax], Antonio Cruz-Mora[aw,ay], Yahveth Cantero-Fortiz[aw,az], Guillermo J Ruiz-Argüelles[aw,ax] and Dorotea Fantl[c]

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ABSTRACT

The aim of this study was to describe clinical and survival characteristics of transplant-eligible multiple myeloma (MM) patients in Latin America (LA), with a special focus on differences between public and private healthcare facilities. We included 1293 patients diagnosed between 2010 and 2018. A great disparity in outcomes and survival between both groups was observed. Late diagnosis and low access to adequate frontline therapy and ASCT in public institutions probably explain these differences. Patients treated with novel drug induction protocols, followed by autologous stem cell transplantation (ASCT) and maintenance, have similar overall survival compared to that published internationally.

ARTICLE HISTORY
Received 25 February 2020
Revised 7 July 2020
Accepted 25 July 2020

KEYWORDS
Multiple myeloma; Latin America; autologous stem cell transplantation; proteasome inhibitor

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Introduction

Multiple myeloma (MM) represents 1% of all cancers and 10–15% of all hematologic malignancies [1–3]. MM is, therefore, one of the most frequent hematologic neoplasms. In the Western world, the age-standardized incidence of MM has been reported to be approximately 5 cases per 100,000 [4,5]. Due to the lack of registries, the real incidence of MM in Latin America (LA) is unknown.

Despite advances in treatment strategies in recent decades, the gold standard therapy for fit/young, newly diagnosed MM patients continues to be induction regimen based on proteasome inhibitors (PI) followed by high dose chemotherapy with autologous hematopoietic stem cell transplantation (ASCT) [6].

The rationale for frontline PI-based combination was assessed in a meta-analysis performed by Sonneveld et al. [7]. This resulted in the recommendation of PI-based induction regimen in different international guidelines (ESMO, NCCN and ASCO). Currently, the standard of care is VRd (bortezomib, lenalidomide and dexamethasone) regimen, although VTd (bortezomib, thalidomide and dexamethasone) or CyBorD (cyclophosphamide, bortezomib and dexamethasone) are also commonly used.

In LA, the access to currently recommended standard of care is very heterogeneous. Lack of access to drugs and/or their financing mainly affects countries where the public health system provides treatment to the majority of the population.

There is scarce data on the baseline characteristics and outcomes of transplant-eligible MM patients in LA. The aim of this study was to make a clinical and survival characterization of transplant-eligible MM patients in different countries of LA, with a special focus on differences between outcomes in public and private healthcare facilities.

Patients and methods

An international multicenter retrospective cohort study was conducted. All members of the Grupo de Estudio Latinoamericano de Mieloma Múltiple (GELAMM) were invited to participate. Demographic, clinical and laboratory data were collected through a standardized form that was sent to all participating centers. Potential patients were identified from each center's databases. Data were obtained from their medical records and were included consecutively in code form. Approvals were obtained from the Ethics committees of all participating institutions.

Consecutive transplant-eligible patients with active MM diagnosed between 2010 and 2018 from Chile, Argentina, Ecuador, Mexico, Colombia, and Uruguay were included.

Baseline characteristics at diagnosis and frontline therapy outcomes, including outcomes of ASCT, were analyzed. Transplant-eligible patients were defined as patients $\leq$65 years old, fit to undergo the transplant procedure. The diagnosis of MM was defined according to the International Myeloma Working Group (IMWG) 2014 criteria [8] and staging was performed in adherence to the International Staging System (ISS) recommendations [9]. Induction therapy, defined as frontline treatment planned at diagnosis and before proceeding to ASCT was evaluated. The 2016 IMWG criteria for evaluating response and progression/relapse were used [10]. Public health in LA is referring to that system that provides health care from the state (from the health or labor Ministry).

Exclusion criteria were lack of minimum information in medical records, a diagnosis of plasma cell leukemia, light-chain (AL) amyloidosis or solitary plasmacytoma, and HIV infection.

Statistical analysis

The baseline characteristics of the patients were planned to be presented descriptively and comparisons between private and public management were made using Student's *t* test, Chi-square (χ^2) or ANOVA, as appropriate. Overall survival was calculated using the Kaplan–Meier curves method. Progression-free survival (PFS) was not calculated. The main reason is that in one of the participating countries (Chile), patients of the public health system can only be transplanted if they achieve a complete remission or very good partial response after first-line treatment. This sometimes leads to the initiation of a second line without progression of the disease, resulting in erroneous data in PFS. Also, second-line options were heterogeneous in the different countries. Comparisons of survival between groups were made by the log-rank test, and Cox regression analysis was utilized to identify baseline characteristics with prognostic value in terms of outcomes. Statistical analysis was performed by using STATA 13 software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results

We included 1293 transplant-eligible MM patients in the study, 363 from Chile, 395 from Argentina, 209 from

Colombia, 45 from Ecuador, 151 from Mexico, and 130 from Uruguay. The baseline characteristics of the patients at diagnosis and therapeutic strategies undertaken are shown in Table 1. Median age was 54 years (range 22–65) and male-to-female patient ratio was 1: 0.9. IgG was the most frequent isotype (57%), followed by light chains (LC) (19%); 74% were classified as ISS II or III. Bone disease was the most frequent myeloma-defining event (64%), followed by anemia (56%), renal failure (24%), and hypercalcemia (16%). Fluorescence *in situ* hybridization (FISH) analysis was performed in only 32% of patients, with del17p being the most frequent anomaly found (10%).

The most frequently used induction regimen was cyclophosphamide, bortezomib, and dexamethasone (CyBorD) (40%), followed by cyclophosphamide-thalidomide-dexamethasone (CTD) (19%), and bortezomib-thalidomide-dexamethasone (VTD) (17%) (Table 1). Median hemoglobin (g/dL), Calcium (mg/dL), and creatinine (mg/dL) was 9.7 in public vs 10.5 in private setting ($p < .001$), 10.3 vs 9.6 ($p < .001$), and 2.4 vs 1.6 ($p = .021$), respectively.

Optimal response (≥very good partial response: VGPR) was achieved in 37% of patients in the CyBorD group, 46% in the VTD group, and 36% in the CTD group.

Only 53% of patients actually received ASCT. Ecuador has the lowest rate of transplanted patients (6%), followed by Chile (26%). The higher rate was found in Argentina, with 87% (Table 2).

Maintenance therapy was administered in 62% of patients, in 57% lenalidomide-based, and in 33% thalidomide-based.

Among study participants, 592 patients (46%) received treatment in public institutions. The proportion of patients treated in the public setting by country is shown in Table 2. Significant differences were found between both groups. Patients treated in the public institutions were more symptomatic at diagnosis, had more advanced disease ($p = .01$), received less

Table 1. Characteristics of the patients at diagnosis according to institution of origin (public or private).

Characteristics	Total $n = 1293$ N°	%	Public setting $n = 592$ (46%) N°	%	Private setting $n = 701$ (54%) N°	%	p value
Age (median, range)	54 (22–65)		54 (22–65)		54 (23–65)		.903
Sex	$n = 1293$	100	$n = 592$	100	$n = 701$	100	
Female	606	47	287	49	318	45	.286
Male	687	53	305	51	383	55	.286
ISS	$n = 1095$	87	$n = 475$	80	$n = 620$	88	
I	290	26	114	24	176	28	.103
II	340	31	136	29	204	33	.130
III	465	43	225	47	240	39	**.004**
Laboratory findings	$n = 1189$	92	$n = 496$	84	$n = 693$	99	
Anemia	665	56	302	61	363	52	**.004**
Renal failure	288	24	151	30	137	20	**<.001**
Hypercalcemia	194	16	127	26	67	10	**<.001**
Bone disease	759	64	386	78	373	54	**.009**
FISH performed	$n = 410$	32	$n = 103$	17	$n = 307$	44	
TP53 (+)	42	10	12	12	30	10	.902
t(14;16) (+)	4	1	2	2	2	0.5	.708
t(4;14) (+)	21	5	6	2	15	5	.284
Induction regimen	$n = 1269$	98	$n = 581$	98	$n = 688$	98	
CyborD	510	40	125	22	385	56	**<.001**
VTD	215	17	71	12	144	21	**<.001**
RVD	31	2	0	0	31	4	**<.001**
CTD	238	19	204	35	34	5	**<.001**
TalDex	110	9	74	13	36	5	**<.001**
Other with novel agents	104	8	58	10	46	7	**<.001**
Others without novel agents	61	5	49	8	12	2	**<.001**
Induction	$n = 1104$	85	$n = 474$	43	$n = 630$	57	
Bortezomib-based	756	68	196	41	560	88	**<.001**
Transplant	$n = 1293$	97	$n = 588$	98	$n = 669$	85	
Performed	669	53	206	35	463	69	<.001
Maintenance	$n = 823$	64	$n = 317$	54	$n = 506$	72	
Performed	518	62	170	54	348	77	**<.001**
Thalidomide-based	179	33	117	69	51	14	**<.001**
Lenalidomide-based	290	57	37	22	251	74	**<.001**
Bortezomib-based	43	8	15	8	28	8	.985
Other	11	2	1	1	10	4	.097

ASCT: autologous stem cell transplantation; CyBorD: cyclophosphamide, bortezomib, and dexamethasone; CTD: cyclophosphamide, thalidomide and dexamethasone; RVD, lenalidomide, bortezomib and dexamethasone; TalDex: thalidomide and dexamethasone; VTD: bortezomib, thalidomide and dexamethasone.
Bold values are statistically significant.

frequently bortezomib-based induction therapy (<0.001), ASCT (<0.001) and maintenance therapy, and received more thalidomide-based maintenance therapy ($p < .001$) (Table 1).

With a median follow-up of 32 months (range 1–113), the 5-year OS was 64% (IC 95% 60 – 67). When comparing public versus private settings, 5-year OS was 46% vs 80%, with a median OS of 56 months vs not reached, respectively ($p < .0001$) (Figure 1). However, in a multivariate analysis, being treated in the public setting was no associated with worse outcome ($p =$,052), when adjusted by ISS, induction treatment, access to ASCT and maintenance. Hypercalcemia (<0.0001), achieving response less than VGPR ($p < .0001$), not undergoing ASCT ($p = .001$), and not receiving maintenance therapy ($p < .0001$) were independent factors associated with worse outcome (Table 3).

Table 2. Characteristics among different countries cohorts.

	Country					
Characteristic	Argentina	Chile	Colombia	Mexico	Uruguay	Ecuador
Total	395	363	209	151	130	45
Centers	12	20	13	2	28	1
Public setting	18%	97%	0%	44%	42%	100%
Private setting	82%	3%	100%	56%	58%	0%
ISS						
I	34%	22%	19%	26%	26%	37%
II	39%	31%	22%	29%	27%	22%
III	27%	47%	59%	45%	47%	41%
Induction						
Bortezomib-based	97%	11%	96%	41%	45%	82%
Maintenance						
Total	71%	52%	76%	67%	22%	72%
Lenalidomide-based	61%	6%	77%	9%	11%	19%
Thalidomide based	8%	91%	5%	70%	70%	74%
Bortezomib-based	7%	0%	16%	9%	16%	3%
Transplant						
Performed	87%	26%	42%	44%	53%	6%

A subgroup analysis regarding patients who get ASCT was performed (Tables 4 and 5). In this subgroup analysis, for the patients who had ASCT, the 5 years OS was 85% for the private group versus 70% for the public group ($p = .007$). For the patients who did not had ASCT, the 5 years OS was 67 vs 30%, respectively ($p < .0001$) (Figure 2).

Table 3. Multivariate analysis of clinical and laboratory factors at diagnosis associated with worse overall survival.

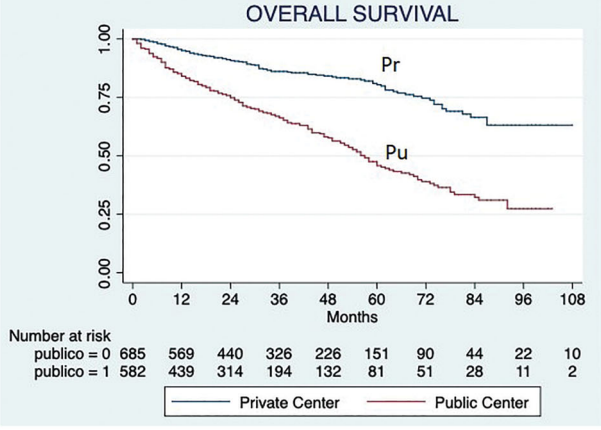
	Multivariate analysis		
Variables	HR (95% CI)	IC	*p* value
Public center	1.46	0.99–2.16	.05
ISS III	1.24	0.85–1.81	.25
Renal failure	1.04	0.67–1.60	.85
Hypercalcemia	2.49	1.57–3.95	**<.0001**
No Bortezomib-based induction	1.43	0.96–2.13	.07
No transplant	0.37	0.25–0.54	**.001**
No VGPR or better	0.55	0.32–0.64	**<.0001**
No maintenance	0.45	0.32-0.64	**<.0001**

VGPR: very good partial response.
Bold values are statistically significant.

Table 4. Characteristics of patients with and without ASCT.

Total patients $n = 1293$	ASCT $n = 669$ (52%)	NO ASCT $n = 624$ (48%)	
Characteristics	N° (%)	N° (%)	*p* value
Age (median, IQR)	55 (49–59)	56 (51-60)	<.001
Sex male	359 (54)	310 (46)	.693
Private setting	463 (70)	206 (38)	<.001
ISS III	212 (32)	246 (39)	<.001
Renal failure	105 / 636 (16)	183 / 538 (34)	<.001
Bortezomib-based induction	513 (77)	279 (46)	<.001
Induction response ≥ PR	572 (89)	286 (66)	<.001
Induction response ≥ VGPR	328 (51)	130 (30)	<.001
Maintenance	428 (70)	90 (39)	<.001

PR: partial response; VGPR: very good partial response.



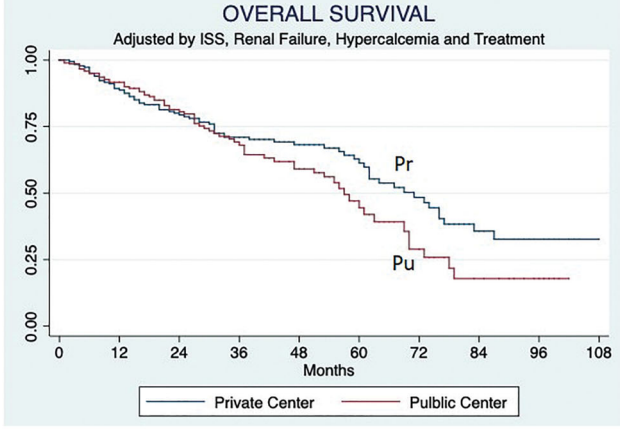


Figure 1. Left: OS between both groups, from patients treated in the public vs private setting. Right: OS adjusted by ISS score, renal failure, hypercalcemia and treatment.

Discussion

We present data that suggest strong differences in clinical presentation and outcomes in MM patients whether they have been treated in the public or private system in LA countries.

Nevertheless, the multivariate model indicates that this covariate is not significant for OS survival per se, while better OS was associated with earlier diagnosis, adequate induction regimen and ASCT. As shown here, only 35% of the public patients had ASCT vs a 69% in the private patients, and bortezomib-based induction was lower in the public setting.

Studies regarding MM outcomes in LA are limited. The first report was published by Hungria et al. in 2017, including 852 Latin American patients from 23 institutions from Argentina, Peru, Chile, Mexico, and Brazil [11]. More recently, Hungria et al. [12] reported treatment patterns and outcomes of 1103 MM patients diagnosed between 2008 and 2015 from seven LA countries. Other data for MM patients in LA come from local efforts, such as the Colombian, Chilean and Uruguayan registries, and from some Mexican centers [13–16].

LA comprises a vast territory with varying gross domestic product among different countries and great heterogeneity in health care facilities [17–22]. An interesting prior study from GELAMM reported the results of a survey that showed a great disparity in treatment availability for MM across different countries in LA, especially between public and private healthcare systems [23].

Our results showed significant differences in NDMM patients, candidates for ASCT treated at private and public health institutions, particularly in the severity of symptoms at diagnosis, ISS staging, access to PI-based induction, access to ASCT and maintenance therapy.

This topic was also discussed by Pessoa de Magalhaes et al. [24], who described that first-line MM chemotherapy regimens in LA for young and elderly patients in public institutions were triplets based on thalidomide, whereas in private institutions, bortezomib based regimens were used. They reported suboptimal treatment (including ASCT) in the public system in 30% of the participating countries. Another example of this was reported by Tarín-Arzaga et al. They compared the results of treatment between the public and private healthcare systems in northeastern Mexico [25]. This study showed that MM was diagnosed at a more advanced stage in the public system, and was usually treated with thalidomide-based

Table 5. Subgroup multivariate analysis: patients that underwent ASCT.

	Multivariate analysis		
Variables	HR (95% CI)	IC	*p* value
Private center	1.8	1.02–3.20	**.04**
ISS III	1.18	0.70–1.98	.53
Renal failure	0.79	0.38–1.67	.55
Hypercalcemia	2.02	0.86–4.77	.1
Bortezomib-based induction	1.53	0.78–2.99	.2
Complete response	0.44	0.26–0.75	**.002**
Maintenance	0.58	0.35–0.95	**.03**

Bold values are statistically significant.

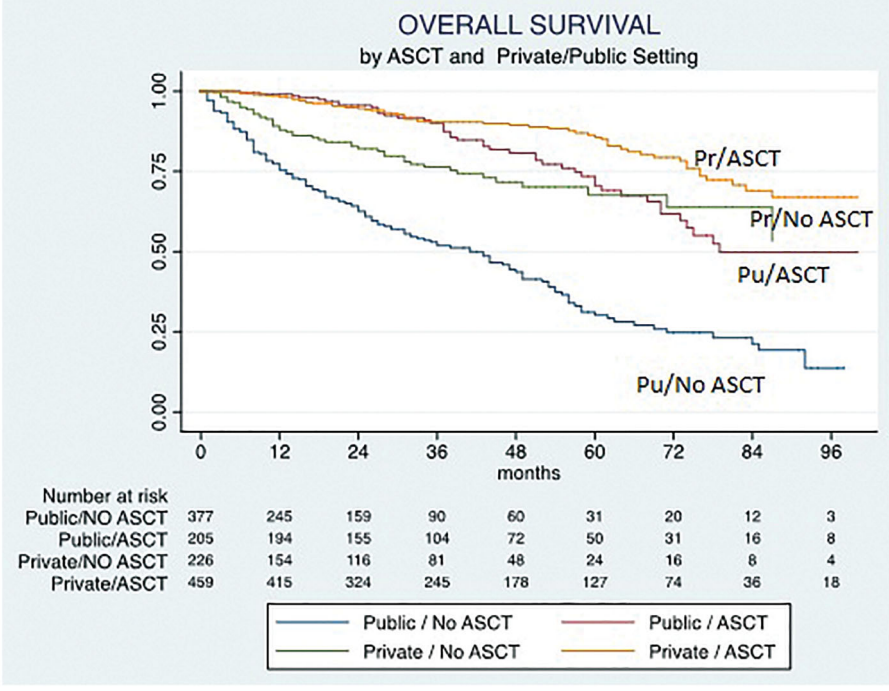


Figure 2. Overall survival by autologous stem cell transplantation (ASCT) and public or private setting.

regimens instead of triplets that include a PI. The outcomes were far better for patients treated in private centers with a very good partial response or a complete response rate of 65 vs. 41% in the public system ($p = .005$) and a median overall survival of 79 versus 41 months, respectively ($p < .001$). Hungria et al. [12] also reported differences in outcomes between both systems, with patients from private centers receiving more bortezomib-based induction (54.3 vs 15.2%) and ASCT (49.4 vs 21.6%) than public centers. Nowadays, the recommended induction regimen is a PI (mostly bortezomib) based induction [7,26]. Our data suggest that this regimen is more likely to be administered in private facilities. Chile was the country with lowest rates of bortezomib-based induction regimen. In this country, CTD was the only treatment approved for these patients in the public system at the time of the study. Although CTD regimen is considered suboptimal, it is still used in LA, especially in the public health system. In the HOLA trial [12], it was the most commonly used treatment. In this study, 19% of the whole cohort was treated with CTD, and 35% of patients from public institutions. CTD use in transplant-eligible patients was also evaluated in Brazil by Crusoe et al. [27] and it was associated with lower survival.

One of the major concerns was the difference between access to ASCT (35 versus 69%). Patients who received ASCT were relatively younger, were more likely to be treated in the private setting, had more bortezomib-based induction regimens, and better responses. They also received more maintenance therapy. On the other hand, patients who did not receive ASCT were more likely to be from the public system, had more advanced disease and renal failure.

ASCT in MM patients in LA is still a very good therapeutic option regarding cost-benefit analysis. Gale et al. showed that about one-half of autologous transplants in LA between 2003 and 2012 were in patients with MM [28]. Nevertheless, access to ASCT in LA is heterogeneous, and many patients do not receive transplantation despite having been considered suitable candidates, particularly in the public setting. We found that only half of ASCT candidates finally underwent the procedure. This is consistent with the results reported by Hungria et al. [11] that reported that 51.2% of eligible patients received ASCT. In our analysis, Ecuador and Chile had the lowest rates of ASCT. In particular, Ecuador has only one transplantation center with five beds for the entire public health system. Chile has two centers in the public setting, but very strict indications for ASCT in MM patients (<60 years old and in ≥VGPR).

OS in this young cohort was lower than expected, mainly due to poor OS in patients from the public system. On the other hand, OS in patients from private centers is comparable with international reports [29].

Maintenance entails better outcomes [30–33]. Two-thirds of our cohort received maintenance therapy. This was associated with better outcomes, regardless of the used drug. In the public setting, 69% was based on thalidomide, whereas in the private setting 74% was lenalidomide-based. Thalidomide is known to cause significant peripheral neuropathy, often leading to treatment discontinuation. Moreover, it has been reported ineffective in patients with high-risk cytogenetics [34,35]. Thus, this strategy (mostly used in public centers) has to be considered suboptimal.

We acknowledge several limitations of our study, particularly due to its retrospective nature. Although several centers were included, public services are underrepresented in some countries (Colombia and Argentina) which may have an impact on the differences reported. These results should be verified including more LA countries to assess the generalizability of our findings

Conclusion

This is the largest study on transplant-eligible patients with MM in LA. A great disparity was seen between public and private healthcare systems regarding burden of the disease at diagnosis, access to novel drugs and outcomes. OS in patients treated with adequate induction regimens, ASCT and maintenance are similar to that reported internationally. Reasons for approximately half of the potential candidates not being transplanted clearly merit further analysis.

Acknowledgments

The authors thank Dr. María Victoria Mateos and Dr. Brian Durie for comments that greatly improved the manuscript.

Disclosure Statement

The authors report no conflict of interest.

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