


Multiple myeloma treatment patterns and clinical outcomes in the Latin America Haemato-Oncology (HOLA) Observational Study, 2008–2016

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Summary

Limited data are available regarding contemporary multiple myeloma (MM) treatment practices in Latin America. In this retrospective cohort study, medical records were reviewed for a multinational cohort of 1103 Latin American MM patients (median age, 61 years) diagnosed in 2008–2015 who initiated first-line therapy (LOT1). Of these patients, 33.9% underwent autologous stem cell transplantation (ASCT). During follow-up, 501 (45.4%) and 129 (11.7%) patients initiated second- (LOT2) and third-line therapy (LOT3), respectively. In the LOT1 setting, from 2008 to 2015, there was a decrease in the use of thalidomide-based therapy, from 66.7% to 42.6%, and chemotherapy from, 20.2% to 5.9%, whereas use of bortezomib-based therapy or bortezomib + thalidomide increased from 10.7% to 45.5%. Bortezomib-based therapy and bortezomib + thalidomide were more commonly used in ASCT patients and in private clinics. In non-ASCT and ASCT patients, median progression-free survival (PFS) was 15.0 and 31.1 months following LOT1 and 10.9 and 9.5 months following LOT2, respectively. PFS was generally longer in patients treated with bortezomib-based or thalidomide-based therapy *versus* chemotherapy. These data shed light on recent trends in the management of MM in Latin America. Slower uptake of newer therapies in public clinics and poor PFS among patients with relapsed MM point to areas of unmet therapeutic need in Latin America.

Keywords: multiple myeloma, epidemiology, Latin America, treatment patterns, progression-free survival.

Ensuring broad access to high-quality oncology care remains an important challenge in Latin America and other developing countries (Strasser-Weippl *et al*, 2015; Cowan *et al*, 2018). Since 2000, the management of multiple myeloma (MM) in the developed world has changed dramatically (Kazandjian & Landgren, 2016). With the introduction of

novel immunomodulatory therapies (e.g., thalidomide, lenalidomide) and proteasome inhibitors (e.g., bortezomib), 5-year relative survival in MM patients improved from 30–35% to 50–55% in the United States and Europe (Kumar *et al*, 2014; Sant *et al*, 2014; National Cancer Institute Surveillance Epidemiology & End Results Program, 2018).

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However, in many Latin American countries, the approval of, and access to, new treatments may be delayed due to cost concerns and resource limitations (Strasser-Weippl *et al*, 2015; Pessoa de Magalhaes Filho *et al*, 2018; Tarin-Arzaga *et al*, 2018).

Limited data are available regarding contemporary MM treatment practices in Latin America. In a large multinational registry of Latin American MM patients diagnosed between 2005 and 2007, first-line therapy did not include an immunomodulatory drug or a proteasome inhibitor for the majority of patients (Hungria *et al*, 2017). The present study builds upon prior research by describing recent trends in treatment patterns, access to care, and clinical outcomes in a large multinational cohort of MM patients.

Methods

Study design

The Haemato-Oncology Latin America (HOLA) Observational Study (ClinicalTrials.gov identifier: NCT02559583) was a multi-centre, retrospective cohort study of patients with selected haematological malignancies seen between 2008 and 2015 at one of 30 clinics in seven Latin American countries: Argentina (5 sites), Brazil (9 sites), Chile (1 site), Colombia (5 sites), Mexico (6 sites), Panama (3 sites) and Guatemala (1 site) (Pavlovsky *et al*, 2016; Chiattoni *et al*, 2016). A list of participating institutions by country and public/private clinic status is provided in Table SI. The primary objectives of the study were to describe patient demographics, treatment patterns and outcomes in Latin American patients diagnosed with MM, chronic lymphocytic leukaemia or non-Hodgkin lymphoma. Participating hospitals were selected based on their experience in providing clinical care for haematological patients, geographic and practice type representativeness, and willingness to comply with study requirements. Data were collected via retrospective chart reviews conducted by trained medical abstractors using standardized data collection forms.

Research funding and ethics statement

The study was reviewed and approved by each participating hospital's Independent Ethics Committee or Institutional Review Board. Because the study was a retrospective chart review that presented minimal risk of harm to patients, at most sites a waiver of informed consent was granted. At sites where a waiver was not granted, the study included only patients who provided written informed consent. The study was funded by Janssen-Cilag.

Study population

In the present analysis, we report on treatment patterns and clinical outcomes for an inception cohort of incident MM

cases diagnosed between 1 January 2008 and 31 December 2015. Patients were required to be ≥ 18 years at MM diagnosis and to have follow-up data for at least 1 year following diagnosis or until death. Participants in clinical trials were not eligible for study inclusion. Follow-up continued until the patient's last clinic visit, death or 31 December 2016, whichever occurred first.

Antineoplastic treatments

Treatment variables of interest included receipt of autologous stem cell transplant (ASCT) and antineoplastic therapies received as first (LOT1), second (LOT2) and third (LOT3) lines of therapy. Treatment start and end dates were captured for LOT1, LOT2 and LOT3; however, ASCT date was not abstracted. Because ASCT is typically given as part of LOT1 in transplant-eligible patients (Hungria *et al*, 2017; Moreau *et al*, 2017; Multiple Myeloma NCCN Guidelines Panel, 2018), our analyses assume that ASCT was part of LOT1. As detailed in Table SII, for each line of therapy (LOT), anti-neoplastic therapeutic regimens were classified as follows: bortezomib-based, thalidomide-based, bortezomib + thalidomide, chemotherapy, corticosteroids only, or newer agents (lenalidomide- or carfilzomib-based).

Baseline characteristics

Data were collected on the following baseline patient characteristics: age, sex, clinic type (public or private), country, International Staging System (ISS) stage (I, II, III, missing) (Greipp *et al*, 2005; Hungria *et al*, 2008), MM clinical signs and symptoms [bone disease (i.e., lesions or fractures), anaemia (haemoglobin <120 g/l), renal disease (serum creatinine >176.8 $\mu\text{mol/l}$), hypercalcaemia (>2.62 mmol/l)], cytogenetic testing results and comorbidity burden. Cytogenetic results were classified as high-risk if del(17p), t(4; 14) or t(14; 16) was detected, standard risk if none of these cytogenetic abnormalities was found; or not documented/missing (Palumbo *et al*, 2015). Comorbidity burden was operationalized as a count of the following major comorbidities: heart disease, diabetes, hypertension, rheumatic disease, neurological disease, other primary malignancy, and human immunodeficiency virus/acquired immunodeficiency syndrome. All covariates were assessed at the time of initial MM diagnosis.

Clinical outcomes

The primary outcome of interest was progression-free survival (PFS) following LOT1 and LOT2, defined as the time interval between the LOT initiation date and disease progression or death. The evaluation of disease progression was based on the treating physician's assessment and/or decision to initiate salvage therapy, as documented in the patient's medical chart. Overall survival (OS) and best therapeutic response (complete response, partial response, stable disease

or progressive disease) following LOT1 and LOT2 were assessed as secondary endpoints. Mortality was ascertained from the patient's medical record. The evaluation of therapeutic response was based on the treating physician's clinical assessment. Neither disease progression, mortality, nor therapeutic response were centrally adjudicated.

Data analysis

Baseline characteristics by ASCT status were described with proportions. PFS and OS were analysed as time-to-event outcomes, with right-censoring at loss to follow-up or the end of the study period (31 December 2016). PFS and OS following LOT1 and LOT2 were assessed separately in non-ASCT and ASCT patients with unadjusted Kaplan–Meier survival analyses and univariate Cox proportional hazards models. In addition, multivariable Cox models were fitted to adjust for baseline covariates including age, sex, calendar year, clinic type (public, private), country (Brazil, Mexico, Colombia, Argentina, other), ISS stage (I, II, III, missing), comorbidity burden (0, 1, 2+ major comorbidities) and anaemia. In modelling PFS and OS following LOT2, the time interval between LOT1 initiation and LOT2 initiation was also included as a covariate. As discussed above, ASCT date was not abstracted; our decision to stratify the LOT1 and LOT2 outcome analyses by ASCT status reflects our assumption that ASCT occurred as part of LOT1. The Cox regression proportional hazards assumption was evaluated through inspection of the Kaplan–Meier survival plots and assessing the statistical significance of covariate interaction terms with time.

Best therapeutic response (complete response, partial response, stable disease, progressive disease) following LOT1 and LOT2 was quantified with proportions. Unadjusted comparisons of therapeutic response across treatment groups were made with chi-square tests.

In comparing PFS, OS and therapeutic response across therapeutic regimens, analyses were restricted to patients who received thalidomide-based therapy, bortezomib-based therapy, or chemotherapy. Patients who received bortezomib + thalidomide, corticosteroids only or newer agents were excluded from comparative analyses because the sample sizes were too small for reliable estimation of PFS, OS, and therapeutic response rates.

Results

Baseline patient characteristics

The study cohort included 1103 eligible patients with newly diagnosed MM and longitudinal follow-up ≥ 1 year or until death and were a subset of the 1518 incident and prevalent MM cases included in HOLA (Fig 1). The median age at diagnosis was 61 years [interquartile range (IQR): 53, 69]; 50.4% were female. In terms of ISS staging, 15.4% were stage I, 21.2% were stage II, 31.5% were stage III and ISS was not

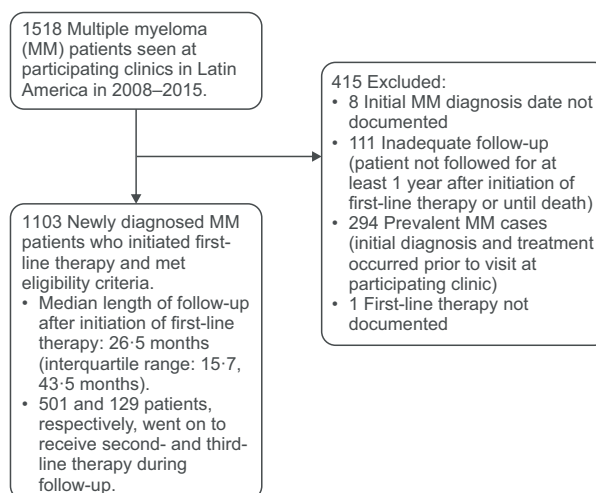


Fig 1. Selection of eligible multiple myeloma patients.

documented for 31.9%. At diagnosis, signs/symptoms of bone disease, anaemia, renal disease and hypercalcaemia were present in 78.5%, 72.7%, 27.0% and 16.7% of patients, respectively. For most patients (80.0%), no documentation of cytogenetic testing was available in the charts. Among the 221 patients with cytogenetic test results, 34 (15.4%) were found to have a high-risk cytogenetics [del(17p), t(4; 14) or t(14; 16)]. Of the 1,103 eligible patients, 769 (69.7%) were initially diagnosed at a participating study clinic; 334 (30.3%) were initially diagnosed elsewhere and referred to a study clinic for treatment.

A total of 374 patients (33.9%) underwent ASCT. On average, ASCT patients were younger and had fewer major comorbidities (Table I). Of the 729 patients who did not receive ASCT, the reason ASCT was not performed, as documented by the treating physician, was advanced age and/or comorbidities for 38.4% of patients, and a lack of resources or the fact that ASCT was not offered by the hospital for 17.8%. For the remaining 43.8% of patients, no reason was explicitly documented in the patient's chart.

Most patients in the sample (55.8%) were treated in public clinics; 44.2% were treated in private clinics. Patients treated at private clinics were more likely to receive ASCT (49.4%) than patients treated at public clinics (21.6%; Table SIII). The four countries contributing the largest number of patients to this study were Brazil (26.0%), Mexico (24.7%), Colombia (23.5%) and Argentina (18.0%); taken together, Chile, Guatemala, and Panama accounted for 7.9% of the study sample. Patients in Argentina and Mexico were slightly younger than patients in the other countries, and a higher proportion of patients in Argentina were ISS stage I (Table SIV).

Treatment patterns

LOT1 was primarily thalidomide-based (54.9%) or bortezomib-based (29.1%); an additional 10.2%, 3.4%, 1.3% and 1.3%

Table I. Baseline characteristics of multiple myeloma patients stratified by autologous stem cell transplant (ASCT) status.

Covariate	No ASCT† (N = 729)	ASCT† (N = 374)	All patients (N = 1103)
Age at diagnosis			
≤64 years	356 (48.8%)	339 (90.6%)	695 (63.0%)
≥65 years	373 (51.2%)	35 (9.4%)	408 (37.0%)
Sex			
Female	360 (49.4%)	196 (52.4%)	556 (50.4%)
Male	369 (50.6%)	178 (47.6%)	547 (49.6%)
Clinic type			
Public	482 (66.1%)	133 (35.6%)	615 (55.8%)
Private	247 (33.9%)	241 (64.4%)	488 (44.2%)
Country			
Brazil	201 (27.6%)	86 (23.0%)	287 (26.0%)
Mexico	237 (32.5%)	35 (9.4%)	272 (24.7%)
Colombia	156 (21.4%)	103 (27.5%)	259 (23.5%)
Argentina	62 (8.5%)	136 (36.4%)	198 (18.0%)
Other (Guatemala, Panama, Chile)	73 (10.0%)	14 (3.7%)	87 (7.9%)
International Staging System (ISS) Stage			
Stage I	82 (11.2%)	88 (23.5%)	170 (15.4%)
Stage II	140 (19.2%)	94 (25.1%)	234 (21.2%)
Stage III	256 (35.1%)	91 (24.3%)	347 (31.5%)
Stage unknown	251 (34.4%)	101 (27.0%)	352 (31.9%)
Myeloma signs/symptoms			
Bone disease	580 (79.6%)	286 (76.5%)	866 (78.5%)
Anaemia	543 (74.5%)	259 (69.3%)	802 (72.7%)
Renal disease	241 (33.1%)	57 (15.2%)	298 (27.0%)
Hypercalcaemia	146 (20.0%)	38 (10.2%)	184 (16.7%)
First-line therapy			
Thalidomide-based	446 (61.2%)	159 (42.5%)	605 (54.9%)
Bortezomib-based	165 (22.6%)	156 (41.7%)	321 (29.1%)
Bortezomib + thalidomide	9 (1.2%)	28 (7.5%)	37 (3.4%)
Chemotherapy	93 (12.8%)	19 (5.1%)	112 (10.2%)
Corticosteroids only	8 (1.1%)	6 (1.6%)	14 (1.3%)
Newer agents	8 (1.1%)	6 (1.6%)	14 (1.3%)
Selected comorbidities‡			
None/not documented	291 (39.9%)	234 (62.6%)	525 (47.6%)
One	270 (37.0%)	105 (28.1%)	375 (34.0%)
Two or more	168 (23.0%)	35 (9.4%)	203 (18.4%)
Cytogenetic testing			
Not done/ not documented	603 (82.7%)	279 (74.6%)	882 (80.0%)
Standard risk	100 (13.7%)	87 (23.3%)	187 (17.0%)
High risk§	26 (3.6%)	8 (2.1%)	34 (3.1%)

*ASCT status reflects whether patients ever vs. never had an ASCT.

†Comorbidities assessed included the following: heart disease, diabetes, hypertension, rheumatic disease, neurological disease, other primary malignancy and human immunodeficiency virus/acquired immunodeficiency syndrome.

‡The following cytogenetic abnormalities were considered markers of high-risk disease: del(17p), t(4:14), or t(14:16).

patients received chemotherapy, bortezomib + thalidomide, corticosteroids only, and newer agents (lenalidomide-based: $N = 13$; carfilzomib-based: $N = 1$), respectively. Non-ASCT patients were most commonly treated with thalidomide-based therapy (61.2%), bortezomib-based therapy (22.6%) or chemotherapy (12.8%), whereas ASCT patients most often received thalidomide-based therapy (42.5%), bortezomib-based therapy (41.7%), or bortezomib + thalidomide (7.5%) as LOT1 (Fig 2).

The median length of patient follow-up following LOT1 initiation was 26.5 months (IQR: 15.7, 43.5); reasons for termination of follow-up were death (32.4%), reaching the end of the study period (16.4%) and cessation of study clinic visits (51.2%). During follow-up, 501 patients (45.4%) and 129 patients (11.7%) initiated LOT2 and LOT3, respectively. Thalidomide-based therapy was less common in LOT2 (24.6%) and LOT3 (21.7%) compared to LOT1 (54.9%). Use of newer agents was more common in patients with

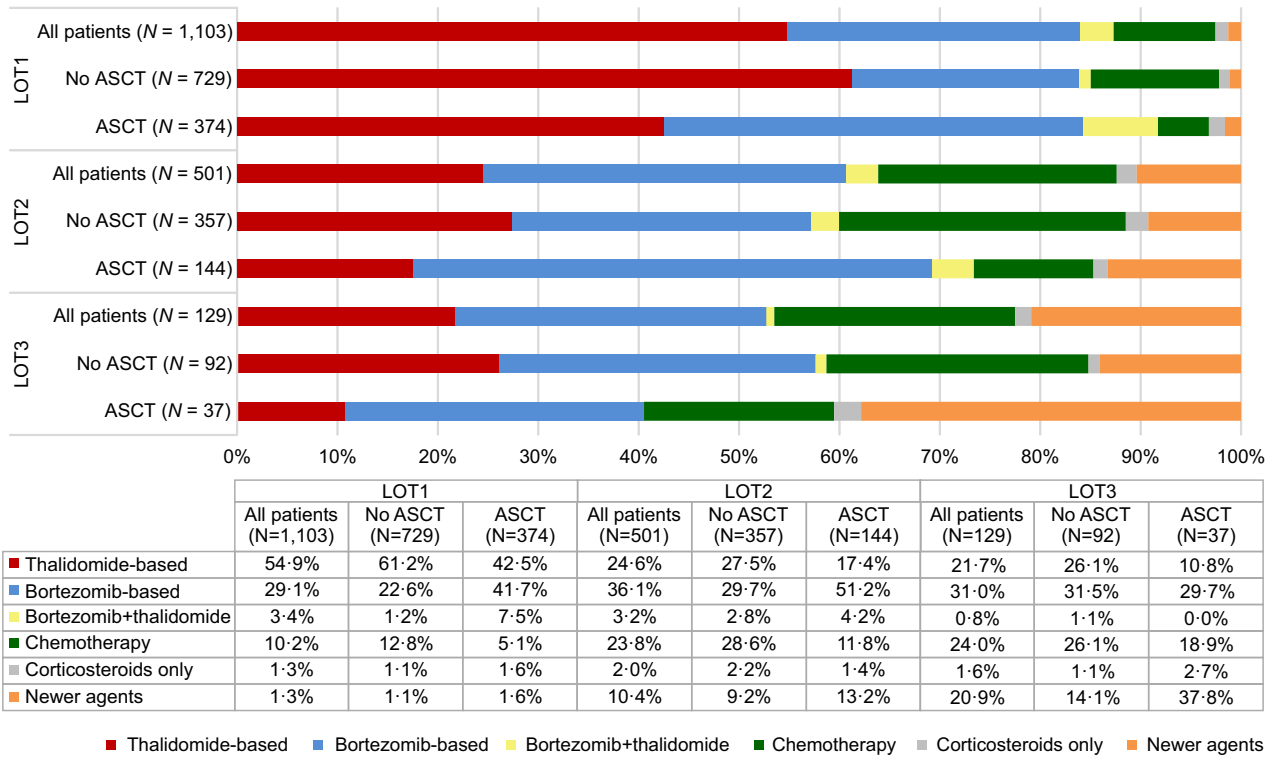


Fig 2. Antineoplastic treatment regimens by line of therapy (LOT) and autologous stem cell transplant (ASCT) status. The newer agents category included lenalidomide- and carfilzomib-based therapies. ASCT status reflects whether patients ever versus never had an ASCT.

relapsed/refractory MM, increasing from 1.3% (lenalidomide-based: N = 13; carfilzomib-based: N = 1) in LOT1 to 10.4% in LOT2 (lenalidomide-based: N = 48; carfilzomib-based: N = 4) and 20.9% in LOT3 (lenalidomide-based: N = 26; carfilzomib-based: N = 1). Antineoplastic regimens by LOT and ASCT status are depicted in Fig 2.

Clinical outcomes following LOT1

Best therapeutic response to LOT1 was documented for 764 patients (69.3%). Among these patients, 30.2%, 45.2%, 8.4% and 16.2% had a complete response, partial response, stable disease and progressive disease, respectively. Patients who underwent ASCT were substantially more likely to have a partial response or better (91.7%) than were non-ASCT patients (64.9%; chi-square P < 0.0001). In general, therapeutic response rates were better with bortezomib-based therapy or thalidomide-based therapy relative to chemotherapy. Best therapeutic response rates by ASCT status and LOT1 treatment regimen are shown in Figure S1.

Median PFS following LOT1 initiation was approximately twice as long in ASCT patients [31.1 months, 95% confidence interval (CI): 25.0, 36.0] than in non-ASCT patients (15.0 months, 95% CI: 13.4, 17.1; log-rank P < 0.0001). In non-ASCT patients, PFS was longer among patients who received thalidomide-based and bortezomib-based therapy

relative to patients who received chemotherapy as LOT1. In ASCT patients, PFS was longer in patients who received bortezomib-based therapy relative to patients who received thalidomide-based therapy or chemotherapy (Fig 3).

Similar associations were observed in the multivariable Cox regression models. In non-ASCT patients, relative to thalidomide-based therapy, those who received chemotherapy as LOT1 had worse PFS [hazard ratio (HR) = 1.60, 95% CI: 1.24, 2.07], and those who received bortezomib-based therapy had non-significantly better PFS (II). In ASCT patients, those who received bortezomib-based therapy had better PFS relative to patients who received thalidomide-based therapy (HR = 0.56, 95% CI: 0.37, 0.85); chemotherapy was associated with non-significantly shorter PFS relative to thalidomide-based therapy (II). No significant violations of the proportion hazards assumption were identified in the Cox models.

Median OS following LOT1 initiation was 79.3 months (95% CI: 77, upper limit not estimable) in ASCT patients, significantly higher than the median of 52.8 months (95% CI: 46.3, 68.6) in non-ASCT patients (log-rank P < 0.0001). In non-ASCT patients, adjusted OS was significantly worse in patients who received chemotherapy as LOT1 relative to patients treated with thalidomide- or bortezomib-based therapy; in ASCT patients, adjusted OS did not differ significantly by treatment regimen (Table SV).

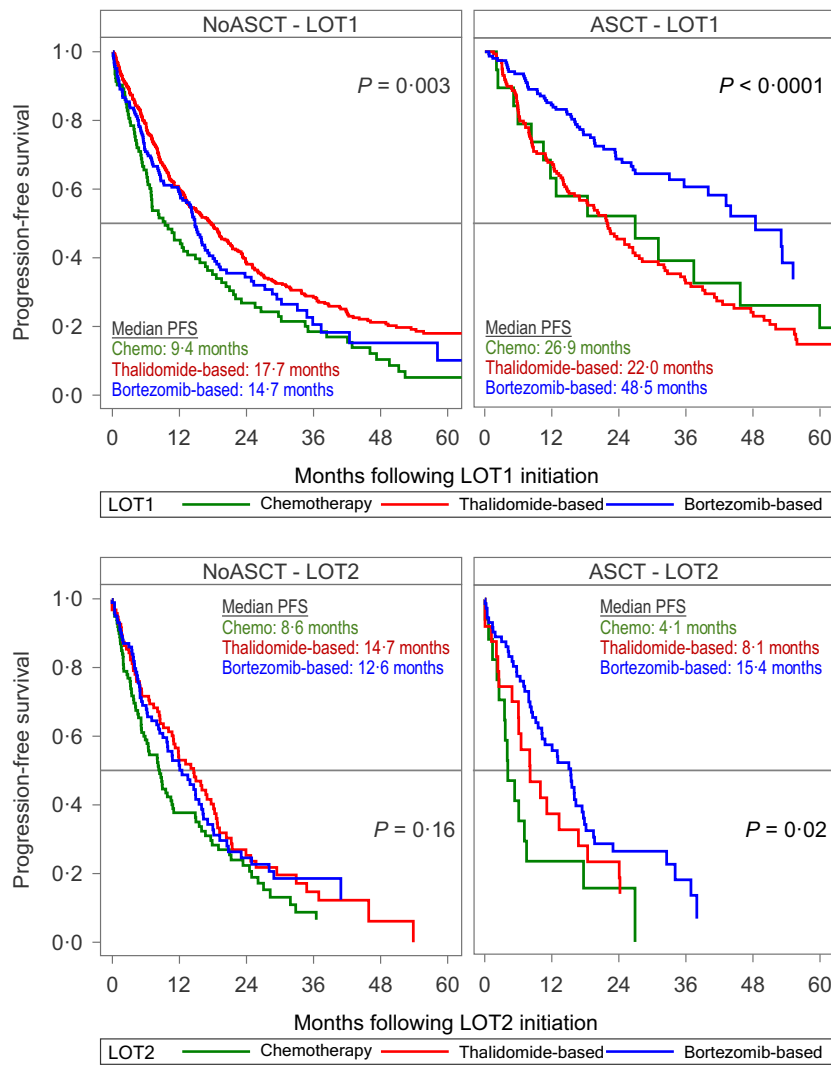


Fig 3. Progression-free survival (PFS) following first-line (LOT1) and second-line therapy (LOT2) by autologous stem cell transplant (ASCT) status. P-values reflect log-rank tests for differences in PFS across patients treated with chemotherapy, thalidomide-based therapy, or bortezomib-based therapy. ASCT status reflects whether patients ever *versus* never had an ASCT.

Table II. PFS and corresponding adjusted hazard ratios following initiation of first- and second-line therapy.

Line of therapy	ASCT status*	Treatment regimen	Median PFS, months (95% CI)	Unadjusted HR† (95% CI)	Adjusted HR‡ (95% CI)
First-line therapy (LOT1)	No ASCT	Thalidomide-based	17.7 (14.0, 20.1)	1.00 (reference)	1.00 (reference)
		Bortezomib-based	14.7 (12.1, 16.6)	1.20 (0.97, 1.49)	0.82 (0.63, 1.06)
		Chemotherapy	9.4 (6.6, 14.8)	1.50 (1.18, 1.91)	1.60 (1.24, 2.07)
	ASCT	Thalidomide-based	22.0 (16.1, 26.5)	1.00 (reference)	1.00 (reference)
		Bortezomib-based	48.5 (40.0, —)§	0.47 (0.34, 0.65)	0.56 (0.37, 0.85)
		Chemotherapy	26.9 (8.3, 45.8)	0.90 (0.53, 1.55)	1.33 (0.67, 2.63)
Second-line therapy (LOT2)	No ASCT	Thalidomide-based	14.7 (10.8, 18.2)	1.00 (reference)	1.00 (reference)
		Bortezomib-based	12.6 (9.1, 16.1)	1.03 (0.74, 1.44)	0.63 (0.43, 0.94)
		Chemotherapy	8.6 (5.7, 10.8)	1.33 (0.96, 1.83)	1.32 (0.94, 1.86)
	ASCT	Thalidomide-based	8.1 (4.9, 16.7)	1.00 (reference)	1.00 (reference)
		Bortezomib-based	15.4 (9.5, 17.4)	0.77 (0.45, 1.31)	0.54 (0.27, 1.07)
		Chemotherapy	4.1 (2.1, 7.5)	1.73 (0.87, 3.43)	2.15 (0.97, 4.78)

ASCT, autologous stem cell transplant; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

*ASCT status reflects whether patients ever vs. never had an ASCT.

†Unadjusted and covariate-adjusted HRs estimated with Cox regression models, as described in the methods section. Patients who received bortezomib + thalidomide, corticosteroids only or newer agents were excluded from the comparative PFS survival analyses due to small numbers.

‡Upper limit of 95% CI not estimable due to censoring.

Clinical outcomes following LOT2

Best therapeutic response was documented for 291 patients (58.1%) who initiated LOT2. Of these patients, 42 (14.4%) had a complete response, 129 (44.3%) had a partial response, 43 (14.8%) had stable disease and 77 (26.5%) had progressive disease. The percentage of patients experiencing a partial response or better was 55.2% and 67.1% of non-ASCT and ASCT patients, respectively, a marginally significant difference (chi-square $P = 0.06$; Figure S1).

The median length of follow-up after LOT2 initiation was 15.5 months (IQR: 6.2, 28.6). Median PFS following LOT2 was 10.9 months (95% CI: 9.0, 14.0) and 9.5 months (95% CI: 7.9, 15.0) among non-ASCT and ASCT patients, respectively, but this difference was not statistically significant (log-rank $P = 0.94$). In non-ASCT patients, PFS was significantly longer in those who received bortezomib-based treatment as LOT2 (HR = 0.63; 95% CI: 0.43, 0.94) and non-significantly shorter in patients treated with chemotherapy (HR = 1.32, 95% CI: 0.94, 1.86) relative to those who received thalidomide-based therapy. In ASCT patients, patients treated with chemotherapy had non-significantly shorter PFS relative to patients treated with thalidomide-based therapy (HR = 2.15, 95% CI: 0.97, 4.78), whereas patients treated with bortezomib-based therapy had non-significantly longer PFS (HR = 0.54, 95% CI: 0.27, 1.07; Table II). No significant violations of the proportion hazards assumption were identified in the Cox models.

Median OS following LOT2 initiation was 37.1 months (95% CI: 28.6, 52.2) in ASCT patients and 48.4 months (95% CI: 33.0, 77.7) in non-ASCT patients, but this difference was

not statistically significant ($P = 0.21$). In both ASCT and non-ASCT patients, adjusted OS following LOT2 initiation was similar in patients treated with thalidomide-based and bortezomib-based therapy, and was non-significantly worse in patients who received chemotherapy as LOT2 (Table SV).

Exploring heterogeneity in initial patient management

Calendar year. Over the course of the study period, use of bortezomib in LOT1 increased markedly in recent years (2014–2015) as compared with 2008–2009 (Cochran-Armitage trend test $P < 0.0001$). For 2008–2011, 9.1% and 13.6% of non-ASCT and ASCT patients, respectively, received bortezomib-based therapy or bortezomib + thalidomide as LOT1; the corresponding figures for 2014–2015 were 34.7% and 81.3%. Use of newer agents continued to be rare in the LOT1 setting, though there was a slight increase over time from 0.4% ($N = 1$) in 2008–2009 to 2.9% ($N = 4$) in 2014–2015 (Fig 4).

Clinic type. Multiple myeloma patients treated at private clinics were substantially more likely to receive ASCT (49.4%) compared to patients treated at public clinics (21.6%). At private clinics 54.3% of patients received bortezomib-based therapy or bortezomib + thalidomide as LOT1 as compared with 15.2% of patients treated at public clinics. Thalidomide-based therapy as LOT1 was predominant in public clinics (71.1%) but was used to treat only 34.4% of LOT1 patients in private clinics (Table SIII). Trends in LOT1 treatment patterns by calendar year and clinic type are shown

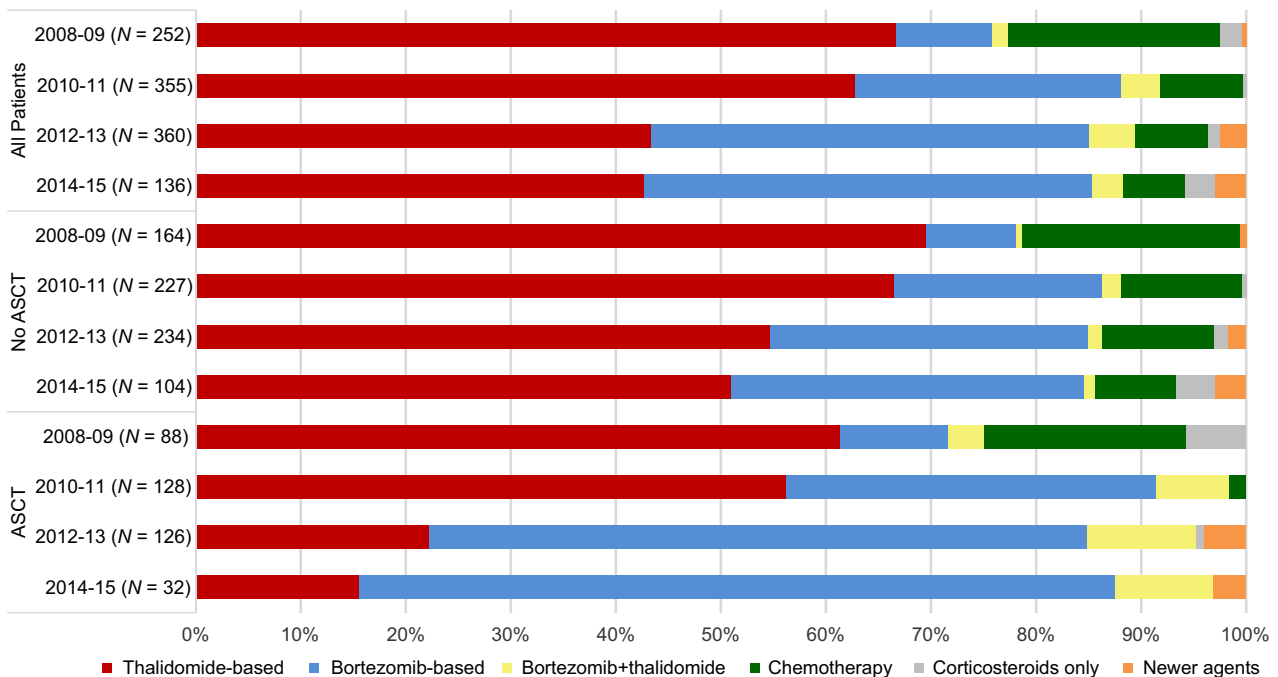


Fig 4. Time trends: first-line therapy (LOT1) by autologous stem cell transplant (ASCT) status and LOT1 initiation calendar year period. The newer agents category included lenalidomide- and carfilzomib-based therapies. ASCT status reflects whether patients ever *versus* never had an ASCT.

in Figure S2. Within the study sample, the increase in utilization of bortezomib-based therapy and bortezomib + thalidomide was considerably greater in private clinics compared to public clinics between 2008 and 2015.

Country. Autologous stem cell transplantation utilization rates were 12.9%, 30.0%, 39.8% and 68.7% in Mexico, Brazil, Colombia and Argentina, respectively. Use of bortezomib-based therapy or bortezomib + thalidomide as LOT1 was high in Colombia (63.3%) and Argentina (45.5%) but was substantially lower in Brazil (16.0%) and Mexico (13.2%). Most participating sites in Argentina and Colombia were private clinics, whereas most sites in Brazil and Mexico were public clinics (Table SIV).

Age. As expected, patients who were ≥ 65 years at diagnosis had a greater comorbidity burden and were substantially less likely to receive ASCT (8.6%) than patients aged < 65 years (48.8%). Older patients were also less likely to receive bortezomib-based therapy or bortezomib + thalidomide as LOT1 (24.0%) relative to patients < 65 years of age (37.4%); patients ≥ 65 years were more likely to receive thalidomide-based therapy or chemotherapy instead. Baseline characteristics and LOT1 therapeutic regimen utilization stratified by age are detailed in Table SVI.

Discussion

In this multi-centre study of Latin American patients diagnosed with MM between 2008 and 2015, LOT1 most commonly consisted of thalidomide-based therapy; however, use of thalidomide-based therapy as LOT1 declined significantly over the study period, particularly among ASCT patients and at private clinics. Conversely, the use of bortezomib-based therapy, bortezomib + thalidomide and newer agents, such as lenalidomide, was higher in more recent years and in the LOT2 and LOT3 treatment settings.

These real-world data provide insights into contemporary practice patterns in the management of MM in Latin America, and contrast with treatment patterns observed in an earlier multinational Latin American registry study (Hungria *et al*, 2017). In that earlier registry study, which enrolled 852 MM patients diagnosed between 2005 and 2007 in Argentina, Brazil, Chile, Mexico and Peru, the majority of patients received chemotherapy, a minority received thalidomide-based therapy, and none received bortezomib as LOT1. In addition, use of ASCT was higher in HOLA (33.9%) than in the earlier registry study (26.9%).

Significant heterogeneity in initial patient management was observed by clinic type (public vs. private) and country in the study sample. Argentina and Colombia—where most patients in the sample were treated at private clinics—were characterized by high rates of ASCT and bortezomib utilization in LOT1 relative to Brazil and Mexico, where most patients were treated at public hospitals. The low rate of

bortezomib use as LOT1 in Brazil and Mexico are consistent with a case series of 65 Brazilian patients diagnosed with MM between 2006 and 2014 and a case series of 77 Mexican patients diagnosed in 2007–2016 who were treated at public hospitals (Minnicelli *et al*, 2015; Tarin-Arzaga *et al*, 2018).

In terms of patient outcomes, our study showed that bortezomib-based and thalidomide-based therapy were associated with superior PFS outcomes following LOT1 and LOT2 relative to chemotherapy. When compared with the other two regimens, bortezomib-based therapy was generally associated with the best PFS, particularly in the LOT1 setting in combination with ASCT. In comparisons of OS, thalidomide-based therapy and bortezomib-based therapy did not differ significantly in covariate-adjusted models, but were generally associated with better OS than chemotherapy. These findings are generally consistent with findings from randomized controlled trials (Sonneveld *et al*, 2012; van Beurden-Tan *et al*, 2017). Among both non-ASCT and ASCT patients, PFS, OS and therapeutic response rates were much worse following LOT2 relative to LOT1. However, it must be emphasized that our study was not a randomized trial and observed differences in outcomes between treatment groups should not be interpreted as causal effect estimates.

Progression-free survival following LOT1 in the HOLA cohort was similar to estimates from the Netherlands-based PHAROS registry study of MM patients diagnosed between 2008 and 2013. In PHAROS, median PFS was 15.2 and 32.0 months in non-ASCT and ASCT patients, respectively (Verelst *et al*, 2018); the corresponding figures in HOLA were 15.0 and 31.1 months. However, estimated PFS was lower in HOLA relative to a contemporary U.S. cohort. Among 2907 U.S. CONNECT Registry MM patients diagnosed between 2009 and 2016, PFS following LOT1 was 21.5 and 44.0 months in non-ASCT and ASCT patients, respectively (Jagannath *et al*, 2018). In HOLA and PHAROS, LOT1 was primarily thalidomide-based; in contrast, LOT1 in CONNECT consisted primarily of proteasome inhibitor (PI)-based therapy or PI + an immunomodulatory drug.

Major strengths of our study include its large sample size, capture of anti-MM treatments and key clinical characteristics, including ISS staging from patients' medical charts and longitudinal follow-up for PFS and OS. Another strength was the extended time period of the study (2008–2016), which allowed us to characterize secular trends in the management of MM in Latin America. To our knowledge, there have been no large epidemiological studies of MM treatment patterns and outcomes in Latin America since the earlier registry study (Hungria *et al*, 2017) of patients diagnosed between 2005 and 2007.

Our study had several important limitations. First, the MM patients included in the study were a convenience sample from 30 participating clinics. Because the sample was not population-based, our results may not be representative of practice patterns within the individual countries or in Latin America as a whole. Practice patterns and access to ASCT

and newer therapeutic agents are likely to differ by country, health insurance status and practice setting (public vs. private) (Pessoa de Magalhaes Filho *et al.*, 2018).

A second limitation was that information on the timing of ASCT was not abstracted. We assumed that ASCT occurred as part of LOT1, which is consistent with clinical practice guidelines, and stratified the LOT1 and LOT2 outcome analyses by ASCT status. In interpreting the LOT1 outcome data stratified by ASCT status, an important consideration is the fact that the ASCT patients must have survived from LOT1 initiation until ASCT. Therefore, differences between ASCT and non-ASCT patients in PFS and OS following LOT1 initiation should be interpreted with caution and not as causal effect estimates.

A third limitation was that data collection in HOLA consisted of retrospective medical chart reviews, not prospective surveillance and follow-up. While the study abstractors were trained and relied on standardized data collection forms, medical record data may be incomplete due to missing records, incomplete chart documentation, and/or the possibility that the patient received care from other clinics. In particular, our analyses of PFS and OS were subject to a large degree of loss to follow-up, which had two important implications. First, data on LOT2 and LOT3 were available for only 501 patients (45.4%) and 129 patients (11.7%), respectively, limiting the precision of our LOT2 and LOT3 analyses. Second, our PFS and OS analyses assume that patients with continued follow-up were representative of the total patient cohort. Our PFS and OS estimates may be overly optimistic if, for example, an out-of-hospital death resulted in loss to follow-up but was not documented in the patient's medical chart. For this reason, readers should be cautious in interpreting our PFS and OS estimates and in comparing them to other studies with more complete follow-up data.

Population-level epidemiological data indicate that the incidence, disease burden and mortality associated with MM are increasing in Latin America, and are likely to continue to do so as average lifespans increase (Curado *et al.*, 2018). Our study provides timely data on contemporary treatment patterns in a large multi-national cohort of Latin American patients with MM. The increase in use of bortezomib-based therapy or bortezomib + thalidomide was notable, particularly in ASCT patients and patients treated at private clinics. However, differences in treatment patterns by country and clinic type (private vs. public) and poor PFS and OS among patients with relapsed MM indicate areas of unmet therapeutic need in Latin America.

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Author contributions

All authors were involved in the study design and/or data interpretation, and drafting, critically reviewing and revising the manuscript. VH, DM, CP, CM, JV, GR, FD, CC, and MC enrolled the patients and acquired the data. TS, GM, MF, MG, YW and PB contributed to research design and data interpretation. EA, JL and YC performed the data analysis and contributed to data interpretation. EA drafted this manuscript with input from all other authors.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. List of participating clinics by country and clinic type.

Table SII. Classification of antineoplastic therapeutic regimens.

Table III. Patient baseline characteristics and first-line therapy, stratified by clinic type.

Table IV. Patient baseline characteristics and first-line therapy, stratified by country.

Table SV. Overall survival (OS) and corresponding adjusted hazard ratios (HRs) following initiation of first- and second-line therapy.

Table SVI. Patient baseline characteristics and first-line therapy, stratified by age at diagnosis.

Figure S1. Best therapeutic response following first-line (LOT1) and second-line therapy (LOT2) by autologous stem cell transplant (ASCT) status.

Figure S2. Time trends: First-line therapy (LOT1) by public/private clinic status and LOT1 initiation calendar year period.

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