A Brazilian Real-life Experience of Multiple Myeloma patients: Final results from the MMyBRAve multi-center study

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Background

- Despite incremental therapeutic improvements for patients with multiple myeloma (MM) over the past two decades, large discrepancies still exist worldwide in outcomes and in terms of access to novel agents and stem-cell transplantation (SCT) [1–3].
- Moreover, the real-world effectiveness of novel therapies may not reflect patient profiles and outcomes from clinical trials. Management of MM in Brazil is subject to constraints that may impact clinical outcomes, and continual assessment of trends in treatment patterns and results in real life is warranted[4].

Objectives

- The objective of MMyBRAve (NCT03506386) was to investigate the demographic and clinical characteristics, as well as the patterns of care and treatment results, for patients with MM treated at hematology/oncology reference centers in Brazil.

Methods

- The eligible patients were aged ≥18 years and had been diagnosed with MM using contemporaneous International Myeloma Working Group (IMWG) criteria between Jan 2008 and Dec 2016.
- Demographic and clinical data were collected from institutional charts retrospectively between Jun 2018 and Aug 2019 using a dedicated electronic case report form.
  - Institutions with potential to include more than 50 patients (from different regions) were selected.
- Treatment and patient evaluation were left to local standards of care.
- Baseline patient and disease characteristics, as well as treatment patterns, were analyzed descriptively.
- The overall survival (OS) was analyzed using the Kaplan-Meier method, and predictors of OS were explored using Cox proportional-hazards model.
- The OS was compared between subgroups defined according to selected baseline characteristics, eligibility to transplantation (Tx) at baseline, and type of institution (public vs private).

Results

- Between Jun 2018 and Aug 2019, data from a total of 943 patients provided by 17 institutions were shown on Table 1.
- Females comprised 46.3% of the patients, and 61.1% were reportedly white. Considering the 792 patients with information on immunoglobulin (Ig) isotype, 57.7% had IgG, 21.2% IgA,16.9% light-chain only, non-secretory in 3.5%, and IgD, IgE or IgM in 0.6%. International Staging System (ISS) stage at diagnosis was I in 19.3%, II in 21.3%, III in 26.6%, and unknown in 32.8%. 491 (52.1%, 95% confidence interval [CI], 48.9% to 55.3%) patients were considered Tx-ineligible at baseline. 452 (47.9%, 95% CI, 44.7% to 51.1%) patients were considered Tx-eligible, and 250 (55.3% of 452; 95% CI, 50.6% to 60.0%) underwent Tx as part of frontline therapy. Overall, after a median follow-up of 63 months, the median OS was 70 months, with OS probabilities of 87% at 12 months, 78% at 24, 70% at 36, 62% at 48, and 55% at 60 months.

Table 1. Baseline demographic characteristics according to type of center

Characteristics	Public (N=519)	Private (N=424)	P-value
Age, median (IQR), years	68 (60-76.8)	69 (61-78)	0.273
Gender, n (%)			
Female	252 (48.6)	185 (43.6)	0.149
Male	267 (51.4)	239 (56.4)	
Race, n (%)			
White	321 (61.8)	255 (60.1)	0.640
Other or unknown	198 (38.2)	169 (39.9)	
Durie-Salmon Stage, n (%)			
I	28 (5.4)	34 (8.1)	0.001
II	84 (16.2)	67 (15.8)	
III	347 (66.9)	241 (56.8)	
Not performed/not available	60 (11.5)	82 (19.3)	
International Staging System stage, n (%)			
I	69 (13.3)	113 (26.7)	<0.001
II	105 (20.2)	96 (22.6)	
III	142 (27.4)	109 (25.7)	
Not performed/not available	203 (39.1)	106 (25.0)	
Hemoglobin, median (IQR), g/dL	9.5 (8.1-11.3)	10.2 (8.7-12.0)	<0.001
Creatinine, median (IQR), mg/dL	1.0 (0.7-1.5)	1.1 (0.8-1.7)	0.013
Calcium, median (IQR), mg/dL	9.5 (8.8-10.5)	9.1 (8.3-9.8)	<0.001
B-2-macroglobulin, median (IQR), mg/dL	2.7 (0.0-6.2)	4.3 (2.5-13.5)	<0.001
Lactic dehydrogenase, median (IQR), U/L	244 (170-343)	220 (153-288)	0.018

IQR, interquartile range

- Table 2 suggest that center type remains an independent prognostic factor; nevertheless, this could be an indication that treatment type (both antineoplastic and ancillary) underlies differences in OS. Therefore, eligibility to transplantation seems to be a stronger prognostic factor for OS than center type, and to confound the association between that outcome and the latter variable (Table 3).

Table 2. Multivariable predictors of overall survival, model with center type

Variable	Hazard ratio for overall survival	P-value
Public vs private center*	0.59	0.002
Age	1.02	<0.001
Haemoglobin	0.88	<0.001
Creatinine	1.16	<0.001
Calcium	1.08	0.023
Durie-Salmon stage I/II vs III	0.63	

* For center type, a hazard ratio <1.00 favours the category "private"

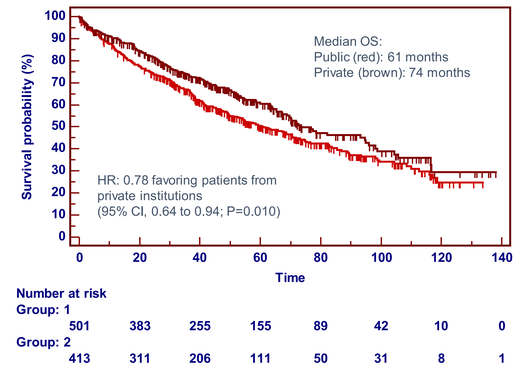
Table 3. Multivariable predictors of overall survival, model with center type and eligibility to transplantation

Variable	Hazard ratio for overall survival	P-value
Public vs private center*	0.77	0.029
Age	1.00	0.192
Haemoglobin	0.88	<0.001
Creatinine	1.13	<0.001
Durie-Salmon stage III vs others	0.69	0.016
Eligibility to transplantation**	0.58	<0.001

* For center type, a hazard ratio <1.00 favours the category "private".
** For eligibility to transplantation, a hazard ratio <1.00 favours the category "eligible".

- Tx-ineligible patients were significantly older and had significantly higher levels of creatinine and lactic dehydrogenase (LDH), and more advanced ISS than Tx-eligible patients. Median OS times were 49 and 93 months for Tx-ineligible and Tx-eligible patients, with a hazard ratio (HR) of 0.52 favoring Tx-eligible (95%CI, 0.43 to 0.63; P<0.001).
- 519 patients came from public institutions, and 424 from private. The former had significantly lower levels of hemoglobin and significantly higher levels of creatinine, calcium and LDH, and more advanced ISS than patients from private institutions.

Figure 1. Overall survival according to type of center, public (red) or private (brown; tick marks represent censoring)



- Median OS in these two groups were 61 and 74 months (Figure 1). Patients from public institutions were more likely to receive melphalan- or thalidomide-based frontline regimens, whereas those from private institutions were more likely to receive bortezomib in frontline.
- Other univariable baseline factors associated with OS were age, hemoglobin, creatinine, calcium, and Durie-Salmon stage. In multivariable analysis for factors associated with OS, all these remained significant, and so was institutions (HR=0.61, P=0.002). Although there was no significant difference in Tx eligibility between public and private institutions (46.1% vs 50.2%; P=0.224) or in the percentage of patients undergoing Tx (24.5% vs 29.0%;P=0.134), adding this variable to the multivariable model for OS suggested that it confounds the association between type of institutions and OS, since Tx eligibility became a stronger prognostic factor (HR=0.586, P<0.001) than type of institutions (HR=0.81, P=0.073).

Conclusions

- Previous experience in real-world MM patient outcomes were quite different but the OS of patients with MM is improving in Brazil[5-7].
- Discrepancies remain in OS for patients from public and private institutions.
- Although the reasons for this finding remain to be ascertained, differential access to novel therapies cannot be ruled out as a determining factor.

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