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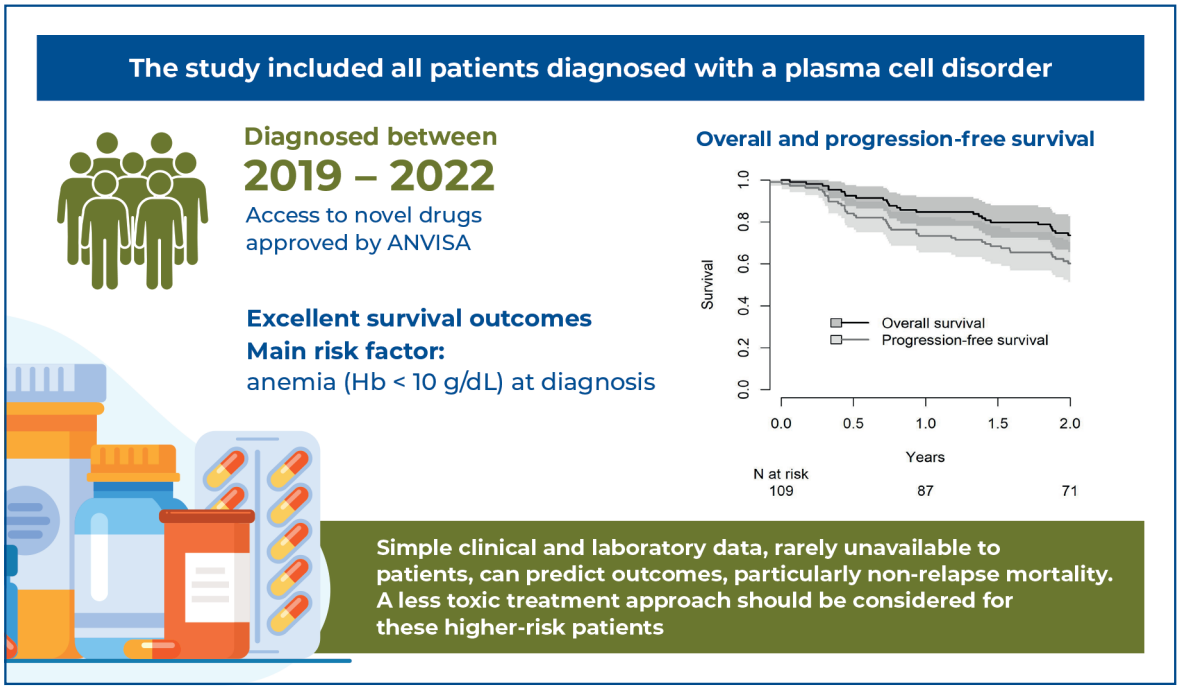
ORIGINAL ARTICLE

Outcomes of multiple myeloma in patients with access to novel drugs



Authors

Leonardo Javier Arcuri, Danielle Ovigli, Cinthya Corrêa da Silva, Fernando Moura, Ricardo Helman, Nelson Hamerschlak

Correspondence

E-mail: leonardojavier@gmail.com

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In Brief

Multiple myeloma is an incurable disease with a poor prognosis. Patients with access to all novel drugs approved by the ANVISA for multiple myeloma were included in this observational study. Three-year overall survival was 69%, highlighting how the natural history of multiple myeloma can be altered by these novel drugs.

Highlights

- Accessibility to novel drugs for multiple myeloma render excellent outcomes.
- Hemoglobin at diagnosis is a significant risk factor.
- Age also impacts outcomes.
- Hemoglobin and age-based model fared better than the International Staging System.

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Outcomes of multiple myeloma in patients with access to novel drugs

Leonardo Javier Arcuri[1], Danielle Ovigli[1], Cinthya Corrêa da Silva[1], Fernando Moura[1], Ricardo Helman[1], Nelson Hamerschlak[1]

[1] Hospital Israelita Albert Einstein, São Paulo, SP, Brazil.

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ABSTRACT

Objective: To report the outcomes of patients with multiple myeloma who had access to novel drugs in Brazil, and to establish a local benchmark. **Methods:** This prospective observational study was conducted at *Hospital Israelita Albert Einstein* in São Paulo, Brazil. We included all patients diagnosed with plasma cell disorders treated between 2019 and 2022. **Results:** We included 109 patients with a median follow-up of 3.7 years. The three-year overall and progression-free survival rates were 69% and 51%, respectively. Multivariate analysis identified age (HR = 1.60 for each additional 10 years, p=0.0025) and hemoglobin levels (HR = 1.25 for each point decrease, p=0.0038) as risk factors for mortality were identified in a model that fared better than the International Staging System. Our results indicate that basic clinical and laboratory data (age and hemoglobin level) also predict overall survival in modern patients with multiple myeloma with access to novel therapies, similar to the International Staging System. **Conclusion:** Simple clinical and laboratory data, which are rarely available to patients, can predict outcomes, particularly non-relapse mortality. Therefore, a less toxic treatment approach should be considered for high-risk patients.

Keywords: Multiple myeloma; Prognosis; Treatment outcome; New drugs

INTRODUCTION

Multiple myeloma (MM) is a hematological cancer classified by the WHO as a malignancy derived from plasma cells. Although it remains incurable, the prognosis of MM has dramatically improved with the introduction of novel drugs[1] like daratumumab and lenalidomide. Nevertheless, autologous hematopoietic cell transplantation still plays a crucial role as a first-line treatment.[2]

Currently, the patients are divided into transplant-eligible and transplant-ineligible groups. Transplant-eligible patients are treated with an induction regimen[3] followed by autologous hematopoietic cell transplantation (usually with high-dose melphalan) and maintenance therapy with a novel drug until progression.[4] In case of progression thereafter, these patients are treated with a new chemotherapy regimen, ideally based on novel drugs, and, depending on the remission time after the first and second transplants.

OBJECTIVE

This study's objective was to report the outcomes of patients with multiple myeloma who had access to novel drugs in Brazil and to establish a local benchmark.

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Associate Editor:
Kenneth Gollob
Hospital Israelita Albert Einstein, São Paulo, SP, Brazil
ORCID: https://orcid.org/0000-0003-4184-3867

Corresponding Author:
Leonardo Javier Arcuri
Guaramomis 480/64
Zip code: 04076-010 - São Paulo, SP, Brazil
Phone: (55 21) 98133-4715
E-mail: leonardojavier@gmail.com

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none.

METHODS

This prospective observational study was conducted at *Hospital Israelita Albert Einstein* in São Paulo, Brazil. Practices in MM were described and characterized for patients who had access to all novel treatments approved by the local regulatory agency, National Health Surveillance Agency (ANVISA - *Agencia Nacional de Vigilancia Sanitaria*), and reported outcomes, thereby establishing a local and national benchmark for patients with MM. We examined all patients diagnosed with plasma cell disorders in accordance with the 4th edition of the World Health Organization Classification of Tumors. The treatment period for these patients spanned from January 1, 2019 to December 31, 2022. The overall and progression-free survivals were estimated using the Kaplan–Meier method. Non-relapse mortality (defined as death in patients without disease progression or relapse) and disease progression were estimated using cumulative incidence curves. Survival and cumulative incidence curves were compared using the log-rank or Gray tests. Multivariate analyses were performed using Cox models, with the final Cox models selected based on the lowest Akaike Information Criterion (AIC). All tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant. All analyses were conducted with R version 4.2.1, utilizing the 'survival' and 'cmprsk' (Subdistribution Analysis of Competing Risks) packages. The local ethics committee of *Hospital Israelita Albert Einstein* approved this study (CAAE: 19927619.5.0000.0071; #4.592.932. This study was conducted according to the principles of the Declaration of Helsinki.

Table 1. Patients' profile

Variable	No Auto HSCT	Auto HSCT	Total	p value
Total	75	34	109	
Median age (IQR)	72 (60.4,77.8)	60.1 (55,63.9)	67.1 (58.6,74.4)	<0.001
Female sex, n (%)	33 (44)	13 (38.2)	46 (42.2)	0.572
Lytic bone lesions, n (%)				0.149
No	33 (44)	10 (29.4)	43 (39.4)	
Yes	42 (56)	24 (70.6)	66 (60.6)	
Bone fracture/lesion, n (%)				0.735
No	51 (68)	22 (64.7)	73 (67)	
Yes	24 (32)	12 (35.3)	36 (33)	
Mean hemoglobin g/dL (SD)	10.8 (2.3)	11.7 (1.9)	11.1 (2.2)	0.072
Median creatinine mg/dL (IQR)	1.1 (0.8,1.3)	0.9 (0.8,1.3)	1 (0.8,1.3)	0.118
Lactate dehydrogenase, n (%)				0.137
High	11 (14.7)	2 (5.9)	13 (11.9)	
Normal	22 (29.3)	16 (47.1)	38 (34.9)	
Unknown	42 (56)	16 (47.1)	58 (53.2)	
ISS, n (%)				0.492
Stage I	21 (28)	14 (41.2)	35 (32.1)	
Stage II	27 (36)	12 (35.3)	39 (35.8)	
Stage III	13 (17.3)	4 (11.8)	17 (15.6)	
Not available	14 (18.7)	4 (11.8)	18 (16.5)	
Novel upfront drugs, n (%)				
Bortezomib	45 (60)	29 (85.3)	74 (67.9)	NA*
Daratumumab	4 (5.3)	4 (11.8)	8 (7.3)	NA*
Lenalidomide	10 (13.3)	8 (23.5)	18 (16.5)	NA*
Any of the three	46 (61.3)	29 (85.3)	75 (68.8)	NA*
Unknown	16 (21.3)	4 (11.8)	20 (18.3)	
Median follow-up/years (IQR)	3.5 (1.8)	4.0 (1.1)	3.7 (1.5)	0.153

*Not calculated because of the different numbers of unknown values.

RESULTS

We included 109 patients with a median follow-up of 3.7 years. As expected, the patients who underwent autologous hematopoietic cell transplantation were younger. There were no other significant differences between the two groups (Table 1).

Upfront treatments included bortezomib (68%), lenalidomide (17%), and daratumumab (7%). At least one of the three drugs was administered in 69% of the patients, and information was not available for 18% (Table 1).

The three-year overall and progression-free survival rates were 69% and 51%, respectively (Figure 1; one-year rates were 85% and 73%, respectively). All univariate analyses are presented in Tables 1S and 2S, Supplementary Material. The multivariable analysis identified age (HR = 1.60 for each additional 10 years, p=0.0025) and hemoglobin levels (HR = 1.25 for each

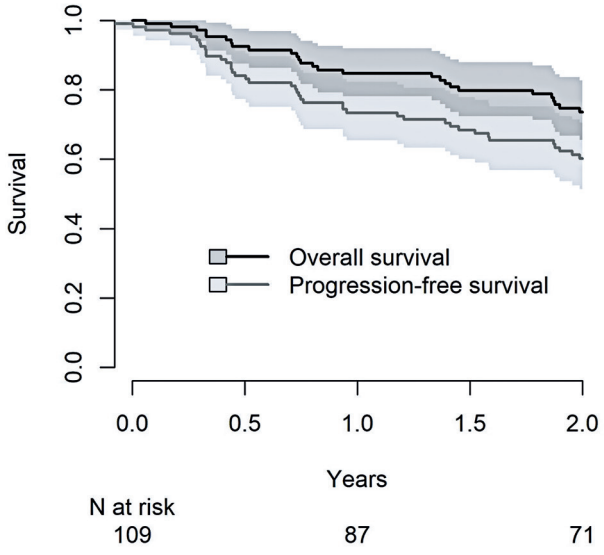

Figure 1. Overall and progression-free survivals

point decrease, p=0.0038) as risk factors for mortality. The plot of smoothing splines for continuous variables (age and hemoglobin) confirmed the linear trend of these variables (Figure 1S, Supplementary Material). In an alternative Cox model, the International Staging System was also significantly associated with mortality (HR = 2.26, stage II; HR = 4.31 for stage III, compared to stage I; p=0.079 and 0.0032, respectively). However, it had a higher AIC (244 compared with 231 for the model including age and hemoglobin; lower AIC values indicate better adjustment of the Cox model). Another alternative model, which categorized age (>70 years) and Hb level (<10g/dL), yielded the best AIC (229), with HR = 3.37, p=0.0032 for age >70 years and HR = 3.17, p=0.0026 for Hb level <10g/dL (Figure 2). Non-relapse mortality accounted for most differences (Figure 3).

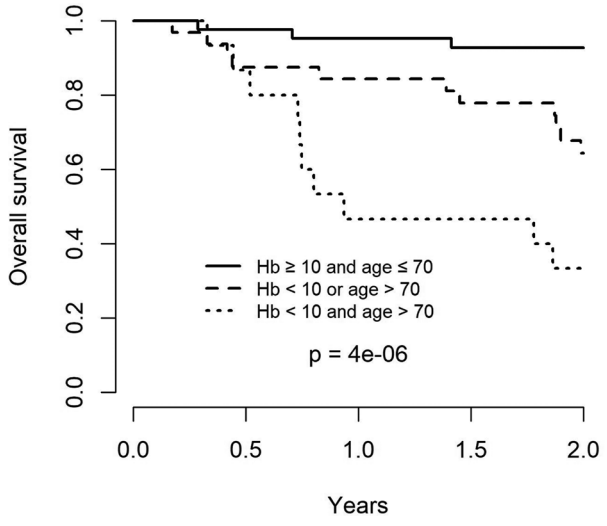

Figure 2. Prognostic groups

In the multivariate analysis for progression-free survival, International Staging System stage III was significantly associated with progression or mortality (HR = 1.86 for International Staging System II, p=0.072; HR = 3.23 for International Staging System III, p=0.0030). Three-year non-relapse mortality rate was 23%, and the one-year progression was 25%.

DISCUSSION

Our results indicate that basic clinical and laboratory data (age and hemoglobin level) also predict overall survival in modern patients with MM with access to novel therapies, similar to the International Staging System.

In our study, age and hemoglobin levels, which were treated as continuous variables, outperformed the International Staging System in terms of overall survival. Our model considered variables as continuous, whereas the International Staging System categorizes them. Information is typically lost when continuous variables are categorized;[5] however, this does not occur when we categorize our continuous variables. The International Staging System[6] published in 2005, is one of the most important prognostic indices for MM. However, treatment options were limited back to 2005, and the revised version of this prognostic index[7] maintained the same framework as the original index while incorporating genetic data. However, the International Staging System predicts progression-free survival. Genetic data require specialized and experienced human resources and may not be feasible in some countries. Easier-to-access prognostic indices are required in developing countries, where genetic data are rarely available in public healthcare services,

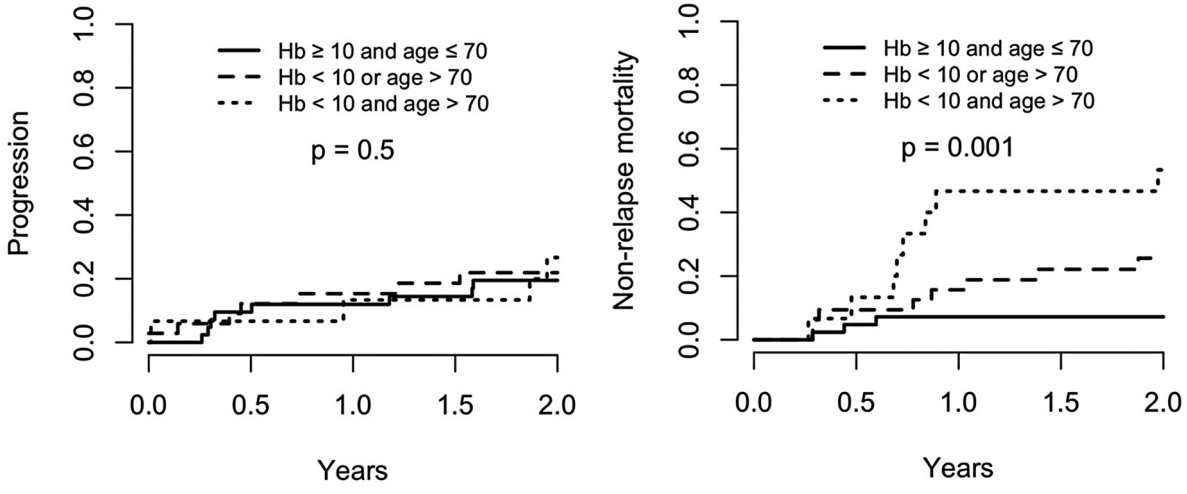

Figure 3. Progression and non-relapse mortality according to prognostic groups

even more so than novel drugs. As most of the higher mortality rates were due to non-relapse deaths, patients >70 years of age with Hb levels <10g/dL at diagnosis should be considered for less toxic therapies.

Most of our patients received bortezomib, an established first-line treatment for MM, in all scenarios. Almost all patients had access to and received upfront treatment in both transplant-eligible and transplant-ineligible settings. Currently, bortezomib is approved in Brazil by CONITEC, which means that it must be incorporated into every public service, such that our results can be extrapolated to Brazilian public hospitals.

Only 7% of the patients received daratumumab upfront. By 2019, daratumumab was already an FDA-approved drug solely for relapsed MM[8] or for the upfront treatment of transplant-ineligible MM, with a subsequent phase 3 trial publication confirming this latter indication.[9] By the end of that year, daratumumab received FDA approval for upfront therapy in transplant-eligible patients based on a randomized trial.[10] Although approval by local regulatory agencies in developing countries is typically slow, we quickly adopted this drug. No new technology is necessary to incorporate daratumumab; only drug acquisition is required. This is in contrast to CAR-T cell therapies[11] and bispecific antibodies[12] which require a significant investment in personnel. When CAR-T-cell therapy and bispecific antibodies are integrated into public services, CONITEC should pursue human resource training.

Our study has several limitations. The data were collected prospectively but partly during the COVID-19 pandemic, which may have increased non-relapse mortality. The follow-up period was relatively short as the study focused on a recent timeframe. However, our follow-up was longer than that has been typically achieved in recent randomized trials involving multiple myeloma.

CONCLUSION

Simple clinical and laboratory data, which are rarely available to patients, can predict outcomes, particularly non-relapse mortality. Therefore, a less toxic treatment approach should be considered for high-risk patients. These findings should be validated in larger cohorts.

DATA AVAILABILITY

After publication, data will be available from the authors upon request—this condition is justified in the manuscript.

ACKNOWLEDGMENTS

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AUTHORS' CONTRIBUTION

Leonardo Javier Arcuri: study design, data acquisition, data analysis, draft writing, and final version approval. Danielle Ovigli, Cinthya Corrêa da Silva, Fernando Moura, Ricardo Helman, and Nelson Hamerschlak: study design, data acquisition, and final approval.

AUTHORS' INFORMATION

Arcuri LA: http://orcid.org/0000-0002-9673-1945
Ovigli D: http://orcid.org/0000-0003-0336-2026
Silva CC: http//orcid.org/0000-0002-8923-5062
Moura F: http://orcid.org/0000-0003-1967-1544
Helman R: http://orcid.org/0000-0002-9730-0696
Hamerschlak N: http://orcid.org/0000-0002-5140-5310

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SUPPLEMENTARY MATERIAL

Outcomes of multiple myeloma in patients with access to novel drugs

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Table 1S. Univariable analyses for overall survival

Variable	HR	p value	95%CI	Number of events	Number	Total fw	1-y OS %	95%CI	p-logrank
Age (Years)	1.04	0.0058	1.01-1.08	28	112	176.7	83	76-91	NA
Sex									
Female	Ref			12	48	73.5	83	73-96	0.90
Male	0.95	0.90	0.45-2.02	16	64	103.2	84	74-94	0.90
Lytic bone lesions									
No	Ref			12	43	67.8	82	70-96	0.61
Yes	0.82	0.61	0.38-1.75	16	69	108.9	84	76-94	0.61
Bone fracture/lesion									
No	Ref			19	75	121.6	81	72-91	0.94
Yes	1.03	0.94	0.47-2.29	9	37	55.1	89	79-100	0.94
Hemoglobin (g/dL)	0.76	0.00053	0.65-0.89	23	95	143.4	81	73-90	NA
Creatinin (mg/dL)	1.16	0.25	0.9-1.5	24	94	143	81	73-90	NA
Lactate dehydrogenase									
High	Ref			6	14	20.6	64	41-99	0.18
Normal	0.49	0.19	0.17-1.41	8	39	55.7	83	72-96	0.18
ISS									
Stage I	Ref			5	36	63.9	97	92-100	0.00089
Stage II	2.68	0.064	0.94-7.63	12	40	60	79	66-94	0.00089
Stage III	6.13	0.0013	2.04-18.47	9	17	19.7	53	33-86	0.00089
Not available	0.80	0.79	0.16-4.16	2	19	33.2	94	84-100	0.00089
Autologous HCT									
No	Ref			27	-	154	NA	NA	NA
Yes	0.24	0.16	0.03-1.77	1	-	22.8	NA	NA	NA

Table 2S. Univariable analyses for progression-free survival

Variable	HR	p value	95%CI	Number of events	Number	Total fw	1-y PFS %	95%CI	p-logrank
Age (years)	1.03	0.013	1.01-1.05	55	108	254.6	71	63-80	NA
Sex									
Female	Ref			24	46	106.2	73	61-87	
Male	0.92	0.75	0.54-1.56	31	62	148.4	70	59-83	0.75
Lytic bone lesions									
No	Ref			18	43	103.9	77	65-91	
Yes	1.43	0.22	0.81-2.54	37	65	150.6	68	57-80	0.21
Bone fracture/lesion									
No	Ref			35	73	172.9	73	63-84	
Yes	1.23	0.45	0.71-2.14	20	35	81.6	68	54-85	0.45
Hemoglobin (g/dL)	0.88	0.035	0.78-0.99	48	91	206.9	70	61-81	NA
Creatinin (mg/dL)	1.13	0.25	0.92-1.38	49	90	205.8	69	60-80	NA
Lactate dehydrogenase									
High	Ref			8	13	26.2	62	40-95	
Normal	0.81	0.62	0.36-1.86	20	38	86.4	66	52-83	0.6
ISS									
Stage I	Ref			14	35	105.4	80	68-94	
Stage II	1.94	0.054	0.99-3.8	22	38	74.4	66	52-84	
Stage III	3.62	0.001	1.68-7.81	13	17	22.6	41	23-73	
Not available	0.82	0.69	0.31-2.15	6	18	52.2	94	84-100	0.0013
Autologous HCT									
No	Ref			47	-	184,4	68	59-79	NA
Yes	0,59	0,19	0.26-1.31	8	-	70,2	100	100-100	NA

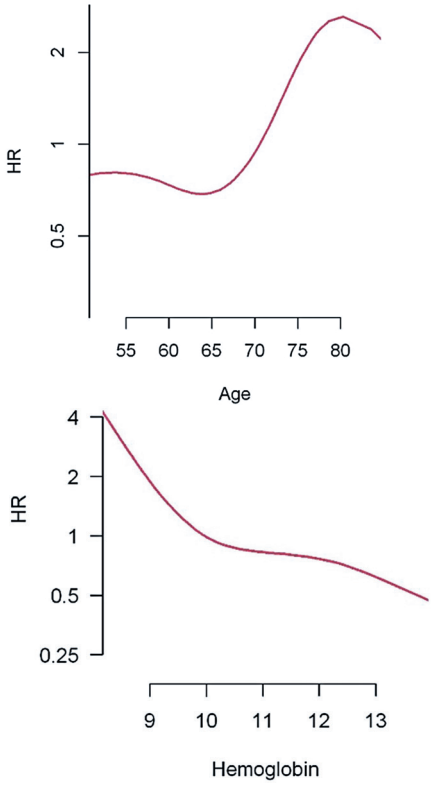

Figure 1S. Smoothing with partial splines