Survival Analysis of Newly Diagnosed Multiple Myeloma Patients after Frontline Autologous Stem Cell Transplantation in a Real-Life Setting

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ABSTRACT

Introduction: Autologous stem cell transplantation (ASCT) is the standard consolidation option for transplant-eligible patients with multiple myeloma (MM). The aim of this study is to report the overall survival (OS) and progression-free survival (PFS) outcomes after frontline ASCT in newly-diagnosed MM (NDMM) patients in a real-world setting.

Methods: We conducted a retrospective, survival analysis of all NDMM patients included in the MM Uruguayan Registry.

Results: We included 151 NDMM patients treated with induction therapy followed by high-dose melphalan and ASCT as consolidation. The median age at diagnosis was 59 years, and the international staging system (ISS) risk groups were ISS-III 32.9%, ISS-II 37.8%, and ISS-I 29.4%. Frontline induction regimens included bortezomib in 61.6% of cases, and maintenance therapy was used in 63.9% of reported cases. With a median follow-up of 42 months, the 36-month OS and PFS for the whole group were 82.4% (95% CI 75.9% to 89.4%) and 63.8% (95% CI 55.6% to 73.3%), respectively, median OS of 98 months and median PFS of 47 months. The 100-month OS and PFS for the entire group were 48.0% (95% CI 34.9% to 66.0%) and 17.3% (95% CI 8.4% to 35.8%), respectively.

Conclusion: ASCT is a feasible, safe, and potent strategy that provides a prolonged median OS and PFS in NDMM patients. This approach can be implemented in low-income countries.

KEYWORDS

multiple myeloma; autologous transplantation; survival analysis; melphalan conditioning

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INTRODUCTION

Multiple myeloma (MM) accounts for 1% of all cancers and 10% of hematologic malignancies, with an incidence of approximately 4/100,000/year (1). In the western world, the incidence of MM varies from 24,280 to 30,330 new cases and 12,650 deaths in 2016, with an age-standardized incidence rate of 5 cases per 100,000 inhabitants (2). In Uruguay, the standardized incidence by age is 2.1 to 3.5 cases per 100,000 inhabitants (3).

Over the last three decades, the introduction of novel drugs has significantly improved the survival rates of MM patients. High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) remains the standard consolidation option for newly diagnosed MM (NDMM) patients who are fit, as demonstrated by the randomized phase three Intergroupe Francophone du Myeloma (IFM) 2009 trial, which reported overall survival (OS) of 88% at three years and progression-free survival (PFS) of 61% in the group that received ASCT (4, 5).

Several factors, including comorbidities, disease biology, and type of induction treatment, have been associated with outcomes after ASCT (6).

ASCT is available to all fit MM patients in Uruguay, regardless of their healthcare provider. However, there are limited local publications focusing on the outcomes of transplantation. Our study aims to fill this gap by reporting the overall survival (OS) and progression-free survival (PFS) achieved using high-dose melphalan and ASCT as consolidation therapy in the Uruguayan population.

PATIENTS AND METHODS

We conducted a retrospective survival analysis of all consecutive active newly diagnosed multiple myeloma (NDMM) patients recorded in the Uruguayan MM Registry between 2009 and 2021 who received high-dose melphalan and autologous stem cell transplantation (ASCT) as consolidative therapy. Patients with incomplete information regarding diagnosis, last control date, relapse/progression or death date, smoldering MM, and plasma cell leukemia were excluded. We analyzed parameters allowing International Staging System (ISS) staging and treatment outcomes evaluation, including ASCT outcomes.

Ethics Committees from participating institutions approved this study.

DEFINITIONS

The diagnosis of MM and response to therapy were defined according to the International Myeloma Working Group (IMWG) criteria (7). High-risk MM was defined using the International Staging System (ISS). Revised ISS (R-ISS) was not reported as cytogenetic analyses were not available in the majority of patients treated before 2015. Overall survival (OS) was defined as the time from diagnosis to the date of death or last contact. Progression-free survival (PFS) was defined as the time from the start of non-radiative therapy to the date of progression, relapse, death by any cause, or last date of follow-up. Early relapse was defined as relapse within the first 12 months from diagnosis.

TREATMENT

Induction therapy was selected by the treating physician, according to current guidelines, reimbursement policies, and drug availability. To simplify the analysis, we classified induction protocols into bortezomib-based regimens (BBR) and non-bortezomib-based regimens (NBBR). ASCT was authorized if partial remission (PR) was achieved after frontline therapy. The standard conditioning regimen used in Uruguayan transplantation centers is melphalan 200 mg/m^2. Mortality due to auto-HSCT was defined as death due to any transplantation-related cause other than disease relapse in the first 100 days after transplantation.

STATISTICAL ANALYSIS

We used Statistical Package for Social Sciences (SPSS) v.25 and R for statistical analysis. Descriptive statistics included quantitative and qualitative variables; quantitative variables were represented with median and interquartile range (IQR) or mean and standard deviation, depending on the normality of distribution determined by the Kolmogorov-Smirnov test. Qualitative nominal or ordinal variables were represented as percentages or proportions. To compare quantitative variables, we used nonparametric methods, and the comparison of proportions was performed with the chi-square test. Survival was analyzed using Kaplan-Meier curves and the Log-rank test, with p-values considered statistically significant when <0.05. For multivariate analysis, we used the Cox regression model, including only those variables with a significant impact observed during univariate analysis.

RESULTS

We analyzed a cohort of 151 patients with active NDMM, with a median age at diagnosis of 59.0 years (IQR 11.0, range 31 to 71) and 61.6% being male. The median follow-up for the entire group was 42.0 months (IQR 42.0, range 5 to 147). Most patients had an advanced Durie-Salmon stage III (70.7%). According to ISS risk staging (n = 143), 32.9% were classified as ISS III, 37.8% as ISS II, and 29.4% as ISS I. Median values for hemoglobin, creatinine, calcium, serum monoclonal component, and bone lytic lesions frequency were 10.0 g/dL (IQR 3.4), 1.0 mg/dL (IQR 0.7), 9.4 mg/dL (IQR 1.1), 2.7 g/dL (IQR 3.6), and 77.5%, respectively. At diagnosis, 6% of patients required hemodialysis, but none continued dialysis at the time of ASCT. The majority of patients had IgG MM (56.3%), followed by IgA (26.4%), light chain (15.9%), and non-secretory (1.3%) MM. Table 1 presents further details on the characteristics of the included patients.

Tab. 1 Characteristics of patients included in the study.

	n	%
Total, n (%)	151	100,0
Age		
Age ≥ 60 years	59	44.7
Sex		
Male	93	61.6
Female	58	38.4
MM Subtype		
IgG Kappa	47	31.1
IgG lambda	38	25.2
IgA kappa	28	18.5
IgA lambda	12	7.9
LC	24	15,9
Non-secretory	2	1.3
ISS Stage (N = 143)		
ISS I	36	29.4
ISS II	48	37.8
ISS III	42	32.9
Laboratory at diagnosis		
Hemoglobin < 10 g/dL	76	50.3
Calcium > 11.5 mg/dL	20	13.2
Creatinine > 2 mg/dL	28	18,5
Lytic lesions	117	77.5
Induction régimen		
BBR	93	61.6
Pretransplant response		
≥ VGPR	85	56.3
Post-transplant response (N = 116)		
≥ VGPR	99	85.3
Relapse <12 months from diagnosis.	13	9.1
Maintenance (N = 122)		
Maintenance	78	63.9
No maintenance	44	36.1

DS; Durie-Salmon; ISS, international staging system; VGPR, very good partial response; MM, Multiple myeloma; BBR, bortezomib-based regimen; OS, overall survival.

INDUCTION REGIMEN

Of the patients included in the study, 61.6% received bortezomib as part of their frontline induction regimen. Among bortezomib-based regimens (BBRs), the most common was CyBorD (cyclophosphamide, bortezomib, and dexamethasone) at 43.7%. Other BBRs used included VTD (bortezomib, thalidomide, and dexamethasone) at 7.3%, VRD (bortezomib, lenalidomide, and dexamethasone) at 6.6%, VTD-PACE (VTD-cisplatin, doxorubicin, cyclophosphamide, and etoposide) at 3.3%, and PAD (bortezomib, doxorubicin, and dexamethasone) at 0.7%. Among non-bortezomib-based regimens (NBBRs), the most common was CTD (cyclophosphamide, thalidomide, and dexamethasone) at 28.5%. Other NBBRs used included TD (thalidomide and dexamethasone) at 8.6%, and others at 0.7%.

RESPONSE RATE

At the time of ASCT, all patients met the local criteria for the procedure, resulting in an overall response rate of 100% (≥ PR). Of these patients, 56.3% achieved a very good partial response (VGPR) or better, while 24.5% achieved a complete response (CR). In 116 patients for whom post-ASCT response was reported, 85.3% achieved a VGPR or better and 54.3% achieved a CR. The rate of CR was significantly higher after ASCT compared to that achieved during induction therapy.

MAINTENANCE THERAPY

Maintenance therapy was reported in 122 patients. The type of maintenance was detailed in 78 patients (63.9%): 29.5% Thalidomide, 42.3% Lenalidomide, 17.9% Bortezomib, and 10.3% others. The duration of maintenance was not reported.

SURVIVAL

For the whole group, the 100-month overall survival (OS) and progression-free survival (PFS) were 48.0% (95% CI 34.9% to 66.0%) and 17.3% (95% CI 8.4% to 35.8%), respectively, with a median OS of 98 months (95% CI 63.8 to 132.2) and a median PFS of 47 months (95% CI 39.4 to 54.6) (Figure 1). Additionally, the 36-month OS and PFS were

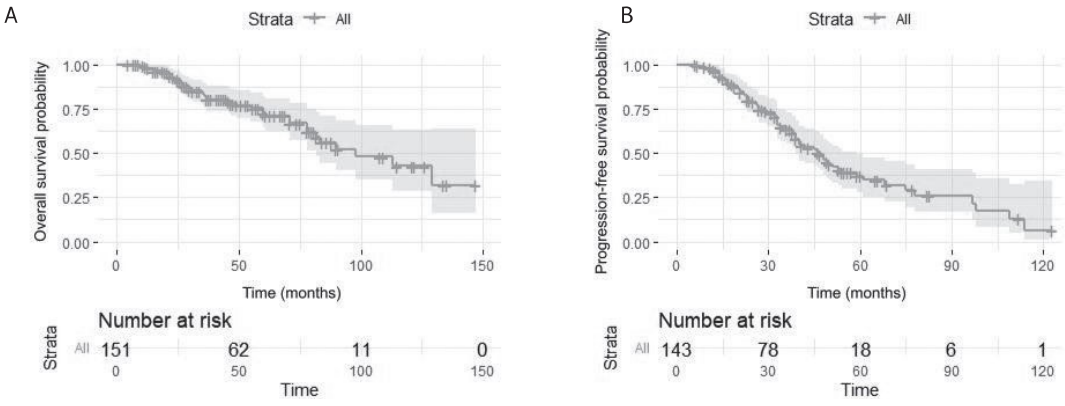

Fig. 1 (A) Kaplan-Meier curve of overall survival for the whole group included; (B) Kaplan-Meier curve of progression-free survival

82.4% (95% CI 75.9% to 89.4%) and 63.8% (95% CI 55.6% to 73.3%), respectively.

When analyzed by the ISS group, patients with ISS-II/III had a reduced 100-month OS (42.0% (95% CI 26.5% to 66.7%) versus 63.0% (95% CI 41.8% to 94.9%), p = 0.076) and PFS (10.2% (95% CI 3.2% to 32.4%) versus 32.3% (95% CI 12.8% to 81.8%), p = 0.010) compared to ISS-I. However, there were no significant differences in median PFS or OS between patients who achieved ≥VGPR after induction and those who achieved PR (p > 0.05).

Regarding the induction therapy used, the 100-month OS for patients who received BBR or NBBR (46.5% (95% CI 32.5% to 66.7%) versus 47.4% (95% CI 27.6% to 81.4%), respectively; p = 0.03). The PFS was not significantly different between these groups (25.2% (95% CI 11.8% to 54.0%) versus 10.6% (95% CI 2.2% to 50.8%), respectively; p = 0.422).

Patients who suffered early relapse (n = 13) had a reduced median overall survival (24 months, 95% CI not calculated as the last event occurred in the 50th percentile), compared to those with relapse after 12 months from diagnosis (98 months 95% CI 64.5 to 131.5).

DISCUSSION

This analysis presents information on the factors that influence survival in a real-life cohort of transplanted patients with newly diagnosed multiple myeloma (NDMM) in Uruguay. Our findings showed a 36-month overall survival (OS) and progression-free survival (PFS) rate of 85.2% and 62.8%, respectively, for the whole group, which is comparable to the results of three randomized clinical trials (IFM2009, EMN02/HO95, and DETERMINATION) that reported improved PFS and OS rates with the use of high-dose melphalan (HDM) and autologous stem cell transplantation (ASCT) compared to a non-transplant strategy. The median PFS survival in these trials ranged from 50 to 67.5 months, with a 5-year OS rate of approximately 80%. As expected, our results also showed a lower OS rate in NDMM patients with ISS-II/III, which was associated with a reduced OS rate of 42% at 100 months (5, 8, 9).

Our results are in line with those reported by the IMWG, in which in 7291 MM patients, albumin level < 3.5 g/dL (OR = 1.36, p = 0.023) and B2m ≥ 3.5 mg/dL (OR 1.86, p < 0.001) had a negative effect on 10-year OS in NDMM transplant eligible patients (10).

We did not find that the use of BBR therapy significantly improved OS and PFS rates. These results could be explained by national policies, since until 2017 standard-risk patients did not receive bortezomib or lenalidomide, which were only authorized for high-risk patients. In consequence, patients receiving novel drugs had a poorer prognosis and this could explain the results, along with the low number of patients. A similar finding was observed in a Mayo Clinic study, using a risk-adapted therapy approach, in which no difference in OS and PFS was found according to the induction regimen (immunomodulatory drug–proteasome inhibitor combination, proteasome inhibitor–alkylator combination, and a doublet therapy). After adjusting for cytogenetic risk, OS between the 3 classes differs from the results of the Southwest Oncology Group trial, where the addition of bortezomib to lenalidomide and dexamethasone resulted in a significantly improved PFS and OS.

We observed an improvement in the depth of response in 29% of patients after ASCT, with a significant increase in complete response (CR) rates from 24.5% to 53.3%. Although the difference was not statistically significant, achieving a more profound response was associated with better PFS and OS rates. Frontline ASCT as consolidation therapy remains a viable option for NDMM patients, particularly in countries with limited access to new frontline therapies.

Early relapse was the most impactful predictor for mortality in NDMMM patients receiving ASCT. In our study, we did not find factors for this condition. Several reasons may explain this finding. First, novel cytogenetic risk factors associated with lower PFS were not studied. Recent staging systems have demonstrated the additive effect of cytogenetic aberrancies such as high-risk IgH translocation (t(4;14), t(14;16), and t(14;20)), del17p, 1q gain/amplification, or del1p, on the risk of death or progression by MM (12-14). Additionally, even when these aberrancies are present, there are conditions with higher risk among them, including a clonal fraction higher than 55% for del17p, mutational status of TP53 and t(4;14) with translocation breakpoint located within the NSD2 gen (Not located upstream NSD2 or in the UTR-5) (15–17).

Second, the duration of maintenance was not reported. Third, the number of patients is low. Fourth, patients with severe renal impairment and/or chronic dialysis have not been transplanted.

The main limitations of this study are the low number of patients and the low availability of cytogenetic analyses. No patients with severe renal impairment and/or dialyses were included. This may have limited, or unintentionally biased, the power of some associations.

Another important limitation regarding the comparison between therapeutic regimens is the reduced number of patients included in each group. It would be important to conduct studies with a higher number of patients to corroborate our results.

CONCLUSIONS

Frontline ASCT as consolidative therapy for NDMM is safe and is associated with prolonged OS and PFS. ISS II-III and early MM relapse (within the first 24 months from ASCT) were associated with shorter PFS and OSn NDMM, regardless of induction therapy. In contrast to the limited access to novel drugs, ASCT is widely available in Latin America. This is a feasible, safe, and potent strategy, providing more than 80% 5-year OS.

CONFLICT OF INTEREST

Authors have no conflict of interest to declare. This research did not receive any specific grant from funding agen-

REFERENCES

1. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol 2020; 95(5): 548–67. Erratum in: Am J Hematol 2020; 95(11): 1444.
2. Gerecke C, Fuhrmann S, Strifler S, Schmidt-Hieber M, Einsele H, Knop S. The Diagnosis and Treatment of Multiple Myeloma. Dtsch Arztebl Int 2016; 113(27–28): 470–6.
3. Kazandjian D. Multiple myeloma epidemiology and survival: A unique malignancy. Semin Oncol 2016; 43(6): 676–81.
4. Al Hamed R, Bazarbachi AH, Malard F, Harousseau JL, Mohty M. Current status of autologous stem cell transplantation for multiple myeloma. Blood Cancer J 2019; 9(4): 44.
5. Attal M, Lauwers-Cances V, Hulin C, et al. Autologous Transplantation for Multiple Myeloma in the Era of New Drugs: A Phase III Study of the Intergroupe Francophone Du Myelome (IFM/DFCI 2009 Trial). Blood 2015; 126(23): 391.
6. O'Shea D, Giles C, Terpos E, et al. Predictive factors for survival in myeloma patients who undergo autologous stem cell transplantation: a single-center experience in 211 patients. Bone Marrow Transplant 2006; 37(8): 731–7.
7. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014; 15(12): e538–e548.5
8. Cavo M, Gay F, Beksac M, et al. Autologous haematopoietic stem-cell transplantation versus bortezomib-melphalan-prednisone, with or without bortezomib-lenalidomide-dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): a multicentre, randomised, open-label, phase 3 study. Lancet Haematol 2020; 7(6): e456–e468. Erratum in: Lancet Haematol 2020; 7(6): e443. Erratum in: Lancet Haematol 2020; 7(11): e785.
9. Richardson PG, Jacobus SJ, Weller EA, et al. Triplet Therapy, Transplantation, and Maintenance until Progression in Myeloma. N Engl J Med 2022; 387(2): 132–47.
10. Usmani SZ, Hoering A, Cavo M, et al. Clinical predictors of long-term survival in newly diagnosed transplant eligible multiple myeloma – an IMWG Research Project. Blood Cancer J 2018; 8(12): 123.
11. Paquin AR, Kumar SK, Buadi FK, et al. Overall survival of transplant eligible patients with newly diagnosed multiple myeloma: comparative effectiveness analysis of modern induction regimens on the outcome. Blood Cancer J 2018; 8(12): 125.
12. Abdallah NH, Binder M, Rajkumar SV, et al. A simple additive staging system for newly diagnosed multiple myeloma. Blood Cancer J 2022; 12(1): 21.
13. D'Agostino M, Cairns DA, Lahuerta JJ, et al. Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: A European Myeloma Network (EMN) Report Within the HARMONY Project. J Clin Oncol 2022; 40(29): 3406–18.
14. Perrot A, Lauwers-Cances V, Tournay E, et al. Development and Validation of a Cytogenetic Prognostic Index Predicting Survival in Multiple Myeloma. J Clin Oncol 2019; 37(19): 1657–65.
15. Thakurta A, Ortiz M, Blecua P, et al. High subclonal fraction of 17p deletion is associated with poor prognosis in multiple myeloma. Blood 2019; 133(11): 1217–21.
16. Corre J, Perrot A, Caillot D, et al. Del(17p) without TP53 mutation confers a poor prognosis in intensively treated newly diagnosed patients with multiple myeloma. Blood 2021; 137(9): 1192–5.
17. Stong N, Ortiz Estevez M, Towfic F, et al. Location of the t(4;14) translocation breakpoint within the NSD2 gene identifies a subset of high-risk NDMM patients. Blood 2023; 141(13): 1574–83.