

Autologous stem-cell transplantation for multiple myeloma: a Brazilian institution experience in 15 years of follow-up

Transplante autólogo em mieloma múltiplo: experiência de um serviço brasileiro em 15 anos de seguimento

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ABSTRACT

Objective: To determine the 5-year post-transplant survival of patients with multiple myeloma. **Methods:** A retrospective study in patients diagnosed with multiple myeloma submitted to autologous bone marrow transplantation at a Brazilian institution, during the period of 1993 to 2007. **Results:** Seventy-three patients were evaluated with a median age of 55 years. Survival in 5 years was 75% (2.4 to 60 months). Statistical analysis demonstrated statistical significance for the applied grade of response prior to treatment with autologous bone marrow transplantation ($p = 0.01$). There was no statistical significance for clinical staging or time of diagnosis (before or after the year 2000). **Conclusion:** Experience in autologous bone marrow transplantation for multiple myeloma at a Brazilian institution demonstrated an evolution consistent with that of medical literature and highlighted the importance of a response to treatment prior to transplantation in the survival of these patients.

Keywords: Multiple myeloma; Transplantation, autologous; Bone marrow transplantation; Survivorship (Public Health)

RESUMO

Objetivo: Determinar a sobrevida de pacientes portadores de mieloma múltiplo em 5 anos pós-transplante. **Métodos:** Estudo retrospectivo em pacientes com diagnóstico de mieloma múltiplo submetidos a transplante autólogo de medula óssea em uma instituição brasileira, no período de 1993 a 2007. **Resultados:** Foram avaliados 73 pacientes com mediana de idade de 55 anos. A sobrevida encontrada em 5 anos foi de 75% (2,4 a 60 meses). A análise estatística demonstrou significância estatística para o grau de

resposta ao tratamento aplicado previamente ao transplante autólogo de medula óssea ($p = 0,01$). Não houve significância estatística para o estadiamento clínico ou período de diagnóstico (antes ou após o ano 2000). **Conclusão:** A experiência na realização de transplante autólogo de medula para mieloma múltiplo, em uma instituição brasileira, demonstrou uma evolução concordante com a literatura médica e destacou a importância da resposta prévia ao transplante na sobrevida desses pacientes.

Descritores: Mieloma múltiplo; Transplante autólogo; Transplante de medula óssea; Sobrevida

INTRODUCTION

Multiple myeloma (MM) is defined as a malignant disorder of plasma cells in which there is secretion of a monoclonal immunoglobulin in the blood and/or urine⁽¹⁾. Its incidence is variable, but it is estimated that it might be responsible for 1% of all neoplasms and for 10% of hematological neoplasms^(2,3).

Multiple myeloma affects primarily the elderly population, with a median age at diagnosis of 67 years, although 3% of the patients are under 40 years of age⁽⁴⁾.

Clinical manifestations of MM are extremely varied, ranging from asymptomatic patients (smoldering myeloma) to clinical emergencies. Therefore, an association of clinical and laboratorial criteria is proposed for the diagnosis, including anemia, renal insufficiency, hypercalcemia and/or bone lesions,

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detection of serum and/or urine monoclonal protein, clonal plasmocyte infiltration in bone marrow and/or presence of a plasmocytoma⁽⁴⁾. In 3% of patients, the monoclonal protein is not detected, and these cases are called “non-secreting” myelomas⁽⁵⁾.

In addition to its classification according to clinical presentation, patients are staged at diagnosis as per internationally standardized criteria, classically, by the Durie-Salmon staging (DSS) and by the International Staging System (ISS)⁽⁴⁾.

DSS classifies patients in three stages according to values of hemoglobin, serum calcium, creatinine, levels of secreted immunoglobulin, and extension of lytic bone lesions. On the other hand, the ISS also proposes three stages, but it is based merely on two laboratorial markers of disease activity: beta-2 microglobulin and albumin⁽⁴⁾.

Currently, cytogenetic assessment is associated with risk stratification. This evaluation may be carried out by karyotype or FISH. The karyotype is used with the objective of detecting deletion of chromosome 13 or hypodiploidy, and FISH for the detection of translocations (4,14), (4,16), or deletion of 17p13. The presence of either one of these genetic markers defines the patient as high-risk⁽⁶⁾.

Since 1980, when the importance of autologous bone marrow transplantation (ABMT) was established as consolidated treatment due to related gains in survival, at the time of diagnosis patients also started to be assessed as to their eligibility for transplantation. For eligible patients, the use of alkylating agents is not recommended in the initial treatment, as they may hinder future mobilization of stem-cells⁽⁷⁾.

Non-eligible patients for ABMT are those subjects with an advanced age (classically over 65 years of age, but this age limit varies from center to center), direct bilirubin > 2.0 mg/dL (34.2 mmol/L), and serum creatinine > 2.5 mg/dL (221 mmol / L), except in cases of stable chronic dialysis and low performance⁽⁸⁾.

The technique employed has been perfected over the 20 years that have separated the initial use of ABMT from new therapeutic advances.

Based on knowledge of immunosuppression caused by the use of alkylating agents and the need for infusion of a salvage marrow to restore its function, melphalan has been considered the drug of choice in induction therapy of autologous transplantation for myeloma⁽⁹⁾.

During the 1990s, when the use of melphalan was well known and widespread, the dose proposed for transplantation was 140 mg/m²; nevertheless, during this decade, higher doses were tested (200 mg/m²), demonstrating that there is no accumulated toxicity and

there is the capacity of increasing overall survival rates, which went from 47 to 60%^(10,11).

The year 2000 is considered an historic mark for myeloma since it was during this period that publications appeared with results of studies performed with the so called “new drugs” (thalidomide, lenalidomide, and bortezomib), which added gains in terms of response to values higher than 70% described in patients with no prior treatment⁽¹²⁾.

Despite the widespread use of these drugs, ABMT remains as the basis for consolidation therapy of MM. Nevertheless, the appropriate moment for its introduction is debatable, besides the importance of a complete response in this context, since the time of maintenance of this response, along with clinical and cytogenetic data, is considered an important prognostic factor⁽¹³⁾.

It is believed that besides reducing tumor burden, ABMT improves the anti-myeloma activity with the use of high doses of melphalan, since the mechanism of action of the alkylating agent is active in progenitor cells, complementing treatment⁽¹⁴⁾.

OBJECTIVE

To report on the survival of patients diagnosed with MM up to 5 years after undergoing ABMT.

METHODS

This is a cohort observational study based on the analysis of data from the medical records of 73 consecutive patients diagnosed with MM and submitted to ABMT at the Hospital Israelita Albert Einstein (HIAE), in São Paulo (SP), between the years of 1992 and 2007.

The data were obtained by retrospective analysis of clinical files retrieved from the Medical Archives and Statistics Service (SAME) at HIAE. Patient progress was documented according to the date of the last follow-up, which included the date of the last out-patient visit or the date of death. The period was established based on the objective of assessing 5-year survival in patients who received transplants over the period of 15 years.

Data on deaths were retrieved by means of an active search with the medical teams listed with the Transplant Service and the hospital admission records.

Seeking to minimize the influence of new drugs on the survival of the sample analyzed in this project, survival related to therapy was divided into two groups, the first of them with patients diagnosed before January of 2000, and the second, after this date.

The cellular mobilization protocol was cyclophosphamide 4 g/m² and colony-stimulating factor (G-CSF). Conditioning was carried out in all 73 cases with melphalan, 65 of them at the dose of 200 mg/m². All the patients received at least 2.0 x 10⁸ nucleated cells/kg when bone marrow was used and at least 2.5 x 10⁶ cells CD34+/kg when peripheral hematopoietic stem-cells were used. Statistical analysis was conducted by means of data coding and application of the Statistical Package for the Social Sciences (SPSS) program. Independent variables (age, subtype of myeloma, staging, myeloma status at the time of transplant, and time of diagnosis) were evaluated by means of Kaplan-Meier's method. The level of confidence adopted was 95%.

RESULTS

During the period of 1992 to 2007, ABMT was performed in 73 consecutive MM patients at the HIAE. In this population, the median age at transplantation was 55 years, and 64% of the patients were male.

DSS data were retrieved in 64 patients and ISS data in 42; the figures are described in detail on Table 1. In stage I of DSS, there were 6.3% (n = 4); in stage II, 59.4% (n = 38); and in stage III, 34.4% (n = 22). Using the classification proposed by ISS, 61.9% belonged to stage I (n = 26); 21.4% to stage II (n = 9); and 16.7% (n = 7) to stage III.

As to the subtype of paraprotein secreted, of the 64 evaluable patients, 73.4% (n = 47) were IgG, 17.2% (n = 11) were IgA, 4.7% (n = 3) were light chain, and 4.7% (n = 3) were non-secreting (Table 1).

Table 1. Overall survival of patients submitted to autologous transplant at Hospital Israelita Albert Einstein, from 1993 to 2007

Characteristics	n	%	Group survival(%)	p value
Durie-Salmon Staging				0.31
I	4	6.3	75	
II A	32	50	84.4	
II B	6	9.4	66.7	
III A	12	18.8	66.7	
III B	10	15.6	50	
ISS Staging				0.24
I	26	61.9	87.7	
II	9	21.4	71.4	
III	7	16.7	57.1	
Immunoglobulin type				0.54
IgG	38	59.4	77.8	
IgG kappa	8	12.5	71.4	
IgG lambda	1	1.6	100	
IgA	7	10.9	71.4	
IgA kappa	2	3.1	100	
IgA lambda	2	3.1	0	
Light chain	3	4.7	66.7	
Non-secreting	3	4.7	100	

ISS: International Staging System.

Of the total number of patients, 49 underwent transplantation after the year 2000 and 15 received 2 procedures. Among the 60 patients with a known prior response to MM treatment before ABMT, in 47.3% (n = 27) it had been complete, and in 53.7% (n = 29) it had been partial. Those transplanted with the disease under progression answered for 6.7% of the total (n = 4).

At the end of 60 months of follow-up, the survival rate was 75%, with a variation of 2.4 to 60 months and the median was not attained (Figure 1). As of D+30 (30 days after the ABMT), two deaths had been verified (2.7%), both of them related to infectious complications. Between days D+30 and D+100, there was one death (1.4%) resulting from a hemorrhagic vascular encephalic accident.

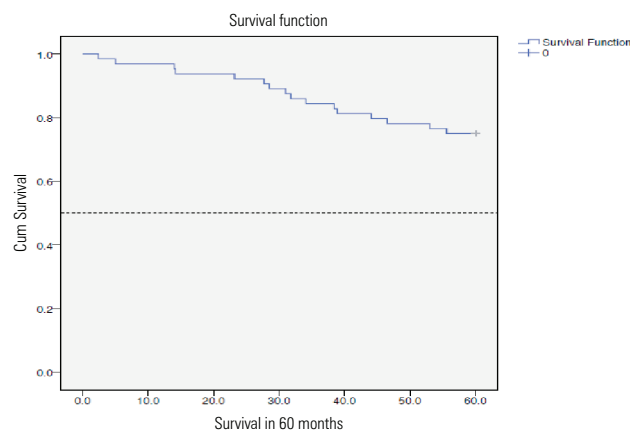


Figure 1. Overall survival of patients submitted to autologous transplant at Hospital Israelita Albert Einstein, from 1993 to 2007

Correlating survival with staging, no statistical significance was observed, whether by DSS (p = 0.31) or by ISS (p = 0.24) (Table 1). Of the total number of 16 deaths evaluated by DSS, 1 patient belonged to stage I, 7 to stage II, and 8 to stage III (Figure 2); of the 8 deaths evaluated by ISS, 3 belonged to stage I, 2 to stage II, and 3 to stage III (Figure 3).

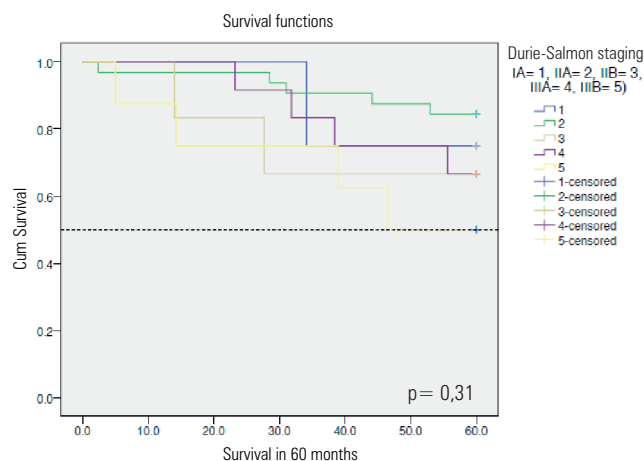


Figure 2. Survival related to Durie-Salmon staging of patients submitted to autologous transplant at Hospital Israelita Albert Einstein

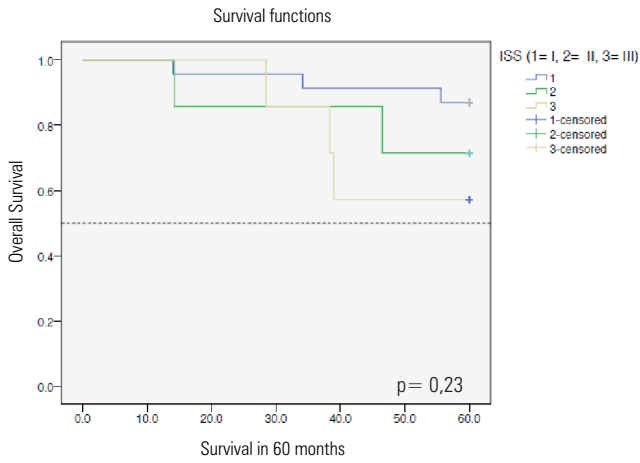


Figure 3. Survival related to ISS staging of patients submitted to autologous transplant at Hospital Israelita Albert Einstein

As to subtype of immunoglobulin secreted, among 15 deaths: 10 were IgG, 4 were IgA, and 1 was light chain. Among non-secretors, there were no deaths during the 60 months. These results did not demonstrate statistical significance ($p = 0.54$) (Figure 4).

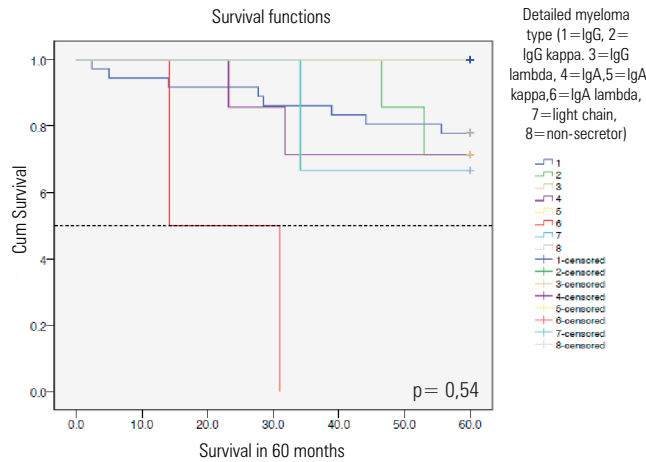
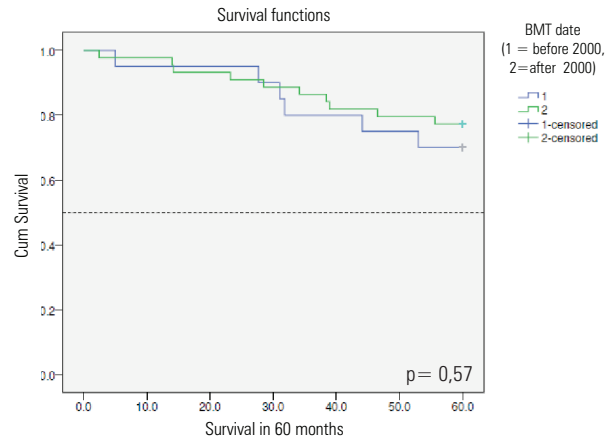


Figure 4. Survival related to subtype of immunoglobulin secreted by patients submitted to autologous transplant at Hospital Israelita Albert Einstein

The time of the diagnosis, meaning, before or after the application of new drugs, also showed no statistical significance ($p = 0.57$) (Figure 5). In the group diagnosed before the year 2000, there was a 30% ($n = 6$) death rate in the total of 20 patients with known status in 60 months. In the group diagnosed after 2000, the death rate was 22% ($n = 10$) of the total of 44 known cases.

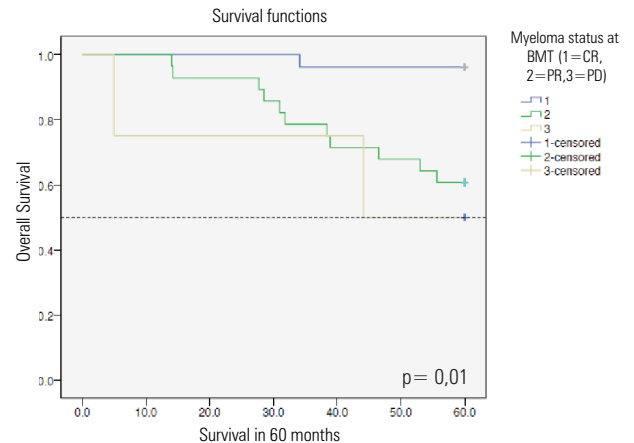
The performance of one or more autologous transplants did not interfere in the related survival ($p = 0.78$), with a 29% (4/14) death rate for patients who underwent ABMT twice, and 24% (12/50) for those who experienced ABMT only once.



BMT = bone marrow transplantation

Figure 5. Survival related to diagnostic period of patients submitted to autologous transplant at Hospital Israelita Albert Einstein

In the assessment of survival in 58 cases, with known prior responses to MM therapy before transplantation, it was noted that, of the total of 26 cases with a complete response, 1 progressed to death; of the 28 with a partial response, 11 progressed to death; and of the 4 with the disease in progression, 2 evolved to death. Progression of the disease was the cause of death in 15 patients. There was statistical significance regarding the response to treatment performed before the transplant and the patient's clinical progress ($p = 0.01$) (Figure 6).



BMT = bone marrow transplantation, CR = complete response, PR = partial response, PD = progression to death

Figure 6. Survival related to type of response to therapy before transplant of patients submitted to autologous transplant at Hospital Israelita Albert Einstein

DISCUSSION

The median age of the population submitted to ABMT in this study was lower than that of the Brazilian population diagnosed with MM, observed in a prior multicentric study in which the median age reported was 60.5 years ⁽²⁾. This fact may be explained by the description of exclusively one sample eligible for ABMT and which, therefore, is expected to be composed of younger patients, as has been demonstrated by literature in this age group: 45 to 52 years ⁽¹⁴⁾.

Regarding staging, it was also noted that the population of this study differed from the previously described Brazilian population in which there was a predominance of advance stages ⁽²⁾. However, once again, this data did not differ from that of medical literature for this group ⁽¹⁴⁾.

Despite the epidemiological similarity with Cavo et al., the survival rate after ABMT was 46% ⁽⁹⁾.

The difference in survival found in this study may be explained by the rate of response prior to treatment. After the 60 months of follow-up, of the 58 patients who could be assessed, 44% were transplanted subjects with a complete response and 48% with a partial response, a fact that proved to be statistically significant ($p = 0.01$).

This relationship between prior response and clinical progress is positively emphasized ⁽¹⁵⁾. According to a study performed by Barlogie et al. with a sample of 668 patients, the 5-year survival rate in cases of MM submitted to ABMT in complete response was 42 to 56% ⁽¹⁶⁾.

The role of the response in evolution of MM was highlighted by the gains obtained after the introduction of the new drugs. Previously, the the treatment regimens used, such as VAD (vincristine, doxorubicin, and dexamethasone), indicated for eligible patients, only demonstrated anti-myeloma activity in half of the cases ⁽¹⁵⁾.

With the objective of minimizing the influence of new drugs in the analysis of clinical progress of the patients studied, the sample of this project was divided, as per the date of diagnosis (before and after the year 2000); nevertheless, this correlation was not statistically significant. Descriptively, however, the survival rate was slightly superior, that is, 70% for the first group and 78% for the second group.

The divisions proposed in this analysis were previously used by Kumar et al. ⁽¹²⁾. In patients over 60 years of age, this author observed a 37% survival rate during the first period, and 52% during the second period. Nonetheless, this study had the exclusive objective of reporting on survival and covered the period from 1971 to 2006. Thus, comparisons between these two samples are not possible ⁽¹²⁾.

CONCLUSION

The experience in the performance of ABMT for MM in a Brazilian institution demonstrated an evolution in agreement with medical literature. Additionally, it highlighted the importance of a response prior to transplantation in the survival of these patients, with a

positive influence for cases with a complete response before undergoing ABMT.

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