Transplante autólogo de células-tronco do sangue periférico no Hospital Universitário de Santa Maria

Autologous peripheral blood stem cells transplantation at the University Hospital of Santa Maria

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RESUMO

Introdução: O principal objetivo deste estudo foi identificar as características clínicas dos pacientes transplantados na instituição e avaliar os resultados obtidos com a infusão autóloga de células-tronco hematopoiéticas do sangue periférico (CTHSP), a mortalidade relacionada ao transplante (MRT) e a sobrevida global (SG). **Métodos:** Através da revisão e avaliação retrospectiva dos prontuários dos 120 pacientes submetidos a transplante autólogo no período de dezembro de 1996 a dezembro de 2011. **Resultados:** Cento e vinte pacientes receberam quimioterapia mieloablativa e resgate com infusões de CTHSP, sendo 78,3% adultos, com mediana de idade de 47 anos e predomínio do sexo masculino. Os diagnósticos foram 32,5% para Mieloma Múltiplo (MM), 35,8% para Linfoma de Hodgkin (LH), 16,7% para Linfoma não Hodgkin (LNH) 4,2% para Leucemia Mieloide Aguda (LMA) e 10,8% para outras neoplasias como Tumor de Wilms, Câncer de Mama Neuroblastoma, Sarcoma de Ewing, Tumor de Testículo, Meduloblastoma, Macroglobulinemia, Amiloidose e Tumor de SNC. A mediana do número de células nucleadas totais infundidas foi de $6{,}46x10^8$/kg e a de células CD34+ foi de $3{,}17x10^6$/kg. A mediana de tempo para recuperação de neutrófilos foi de 10 dias e para plaquetas, de 12 dias. Foi encontrada uma correlação entre a quantidade de células CD34+ infundidas e a recuperação de neutrófilos e plaquetas. Para o grupo em geral, a MRT encontrada foi de 5%, e a probabilidade de SG em cinco anos de 55,1%. **Conclusão:** Os resultados obtidos com os transplantes autólogos em nossa instituição são semelhantes aos descritos na literatura internacional.

UNITERMOS: Célula-tronco de Sangue Periférico, Transplante, Mortalidade Relacionada ao Transplante, Sobrevida Global.

ABSTRACT

Introduction: *The aim of this study was to identify the clinical characteristics of patients transplanted in the institution and evaluate the results obtained with the autologous infusion of hematopoietic stem cells from peripheral blood (PBSC), transplant-related mortality (TRM) and overall survival (OS).* ***Methods:*** *A review and retrospective assessment of the charts of 120 patients who underwent autologous transplantation from December 1996 to December 2011.* ***Results:*** *One hundred and twenty patients received myeloablative chemotherapy and rescue with infusions PBSC, of whom 78.3% were adults, with a median age of 47 years and male predominance. The diagnoses were 32.5 % for Multiple Myeloma (MM), 35.8% for Hodgkin lymphoma (HL), 16.7 % for non-Hodgkin lymphoma (NHL), 4.2 % for Acute Myeloid Leukemia (AML), and 10.8% for other cancers such as Wilms Tumor, breast*

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cancer, neuroblastoma, Ewing's sarcoma, Testicular Tumor, medulloblastoma , macroglobulinemia , amyloidosis and CNS tumor. The median number of total nucleated cells infused was 6.46 x10^8/kg and of CD34+ cells was 3.17 x10^6/kg. The median time for neutrophil recovery was 10 days and for platelets 12 days. A correlation was found between number of CD34+ cells infused and recovery of neutrophils and platelets. For the overall group, the MRT was found to be 5% and the probability of OS at five years was 55.1 %. ***Conclusion:*** *The results obtained with autologous transplantation at our institution are similar to those described in the international literature.*

KEYWORDS: Peripheral Blood Stem Cell, Transplantation, Transplant Related Mortality, Overall Survival.

INTRODUCTION

Haematopoietic stem-cell transplantation is indicated as part of the treatment of haematological malignancies, but also to solid tumors treatment (1). It has become a more frequent therapeutic procedure with stem cells collected from bone marrow, peripheral blood or umbilical cord blood. The advantages of using peripheral blood stem cells instead of bone marrow cells include a faster hematopoietic recovery, fewer transfusions of platelets and red blood cells, shorter antibiotic therapy, no use of general anesthesia or invasive techniques, such as in bone marrow collection in the operating room (2,3).

It is estimated that 50 to 60,000 bone marrow transplantation procedures are performed every year worldwide. Considering the autologous transplants, peripheral blood is used in 90% of cases. After chemotherapy by mobilization, the hematopoietic stem cells (HSC) are collected and can be kept preserved for several years until the time of transplantation(4). The minimum dose of CD34+ cells/kg necessary to restore hematopoiesis has yet to be established, however, 2.0-2.5x10^6/kg is considered the minimum acceptable dose(5).

The prognosis of the transplantation patients has improved in recent decades due to the development of support treatment, reducing the mortality rate. Nevertheless, relapse of the original malignancy remains the most frequent cause of treatment failure (4).

This study aimed to evaluate the PBSC infusion, transplant-related mortality (TRM) and overall survival (OS), as well as to know the characteristics of the population served in the Bone Marrow Transplantation Center (BMTC) and the Treatment Center for Children and Adolescents with Cancer (CTCriaC) at the University Hospital of Santa Maria (HUSM).

METHODS

The study analyzed and evaluated 120 medical records of patients submitted to an autologous transplantation assisted in the BMTC and CTCriaC at the Hematology-Oncology Department of the HUSM, from December 1996 to December 2011. Variables included gender, age, diagnosis, the total nucleated cell count and the number of CD34+ cells infused, days of neutrophil and platelet engraftment, TRM and OS.

After conditioning high-dose chemotherapy (HDC), PBSC previously harvested were cryopreserved in the Cryopreservation Laboratory of the Hematology-Oncology Service of HUSM in a cooling chamber with programmable freezing rate (Cryoson BV-6, Germany), using dimethyl sulfoxide (DMSO) as the cryoprotector agent in the concentration of 10%. The bags containing the HSC were stored in liquid nitrogen containers in the steam phase until the transplantation and after thawed they were infused immediately. This day was set as day zero (D0) for the transplantation. The ideal number of CD34+ cells used to perform the autologous transplantation was 2.0 x 10^6/kg.

The day of the bone marrow engraftment was considered when the absolute neutrophil count reached ≥ 500/μL in the peripheral blood for two consecutive days and a platelet count > 20,000/μL for a week, without requiring transfusion.

Transplant-related mortality (TRM) rates included all deaths until day +100, independently from the cause. Overall survival rates comprised those who survived until December 31, 2011, regardless of disease relapse or other complications.

This study was approved by Ethics in Research Committee of the Federal University of Santa Maria (UFSM) under the number 0106.0.243.000-11 (06/14/2011).

Statistical Analysis

A descriptive analysis of the study variables were carried out. The Kruskal-Wallis test was used to analyze data. For nominal variables the Chi-square test was used. Spearmans correlation coefficient was applied for correlation analysis. Survival curves were made using the Kaplan-Mayer method. The groups were compared using the Log-Rank test. A P value of < 0.05 was considered significant. The variables collected were stored in a database (Excel ® 2007) and analyzed using the Statistical Package for Social Science (SPSS), version 15.0.

RESULTS

Population characteristics

A total of 120 patients were treated with autologous peripheral blood stem cells transplantation (PBSCT). Among the total, three patients underwent two procedures, total-

ing 123 infusions. Forty-nine patients (40.8%) were female, seventy-one (59.2%) male; being 78.3% adults (median 47 years). The case group consisted of 39 patients with MM (32.5%), 43 with HL (35.8%), 20 with NHL (16.7%), 5 with AML (4.2%), 13 with other neoplasias (10.8%) - 2 Wilms tumor, 1 testicular tumor, 3 Ewings Sarcoma, 2 Breast cancer, 1 Neuroblastoma, 1 Meduloblastoma, 1 Macroglobulinemia, 1 Tumor of the Central Nervous System (CNS), 1 Amyloidosis) (Table 1).

Infusion of PBSC

The minimum and maximum count of total nucleated cells infused was $0.55x10^8$/kg and $52.96x10^8$/kg (median $6.46x10^8$/kg), respectively. The minimum and maximum count for the infused CD34+ cells was $1.35x10^6$/kg and $3.94x10^6$/kg (median $3,17x10^6$/kg), respectively.

As for the diagnosis, the minimum and maximum counts of infused CD34+ cells were for MM 1.98 and $13.78x10^6$/kg; for HL 1.49 and $6.90x10^6$/kg; for NHL 1.72 and $5.45x10^6$/kg; for AML 1.35 and $10.81x10^6$/kg; and other neoplasias 1.97 and $23.4x10^6$/kg, respectively.

The median time observed between transplantation and diagnosis according to the base disease, was significantly lower for MM, when compared with the other groups (P = 0.022).

Table 1 – Characteristics of transplant patients.

Variables	Frequency (N)	Percentual (%)	P-value
Gender			
Female	49	40.8	
Male	71	59.2	0.045
Total	120	100	
Age			
≤ 21	26	21.7	<0.0001
>21	94	78.3	
Diagnosis			
MM	39	32.5	
HL	43	3.,8	
NHL	20	16.7	<0.0001
AML	5	4.2	
Other Neoplasias	13	10.8	

The median time period between harvesting and transplantation i.e., the storage period of HSC in liquid nitrogen (vapor phase) was 81 days (9 to 2738 days).

Post-PBSCT Recovery

The mean time period for neutrophil recovery was 11.15 days (7 to 28 days) and the mean platelet recovery was 14.04 days (8 to 79 days). It was observed that three patients did not achieve platelet engraftment; one patient had AML and the other two, NHL.

For neutrophil recovery day, the difference found was between AML and other diagnoses (P = 0.001). The recovery of neutrophil in MM was between days 9 and 18 (mean 11.27 days), in HL between days 8 and 20 (10.26), in NHL days 9 and 18 (11.25), in AML between days 10 and 28 (17) and for other neoplasias between days 7 and 17 (11.27). Platelet recovery occurred between days 9 and 26 (mean 12.37 days) in MM, between days 9 and 21 (12.48) in HL, between days 9 and 21 (14.28) in NHL, between days 9 and 79 (43) in AML and between days 8 and 32 (16.64 days) for other neoplasias (Table 2).

Spearman's rank correlation test identified a negative correlation between the amounts of infused CD34+ cells and neutrophil (-0.299 and P = 0.001) and platelet engraftment (-0.194 and P = 0.041) i.e., the greater the number of infused CD34+ cells, the shorter the time of neutrophil and platelet engraftment. Between the amount of total nucleated cells infused and neutrophil and platelet engraftment there was a weak positive correlation (0.184 with P = 0.045 and 0.263 with P = 0.004, respectively).

Transplant Related Mortality and Overall Survival

TRM found in the group was 5% (6/120): 1 MM, 2 HL, 3 other neoplasias (Amyloidosis, Wilms Tumor, Neuroblastoma). Separated according to the disease, TRM was 2.5% for MM, 2.3% for HL and 23% for the group with other neoplasias. For NHL and AML, there was no information regarding TRM.

In this study, the median time for OS was approximately 7.74 years, and SD= 2.041. In one year, the survival probability was 79.8%, SD = 0.038. In five years, 55.1%, SD = 0.051 (Figure 1).

The OS by diagnosis found was:

Table 2 – Comparison between transplantation variables and diagnosis.

Mean variables- (SD)	MM	HL	NHL	AML	Other neoplasias	P-value
Infused TNC (10^8/kg)	6.03 (5.97)	9.55 (6.78)	9.42 (5.66)	9.09 (9.67)	14.66 (12.88)	0.001
Infused CD34+ cells (10^6/kg)	4.33 (2.43)	3.68 (2.19)	3.20 (1.13)	4.88 (4.29)	5.84 (6.14)	0.297
Neutrophil recovery day+	11.27 (1.72)	10.26 (1.90)	11.25 (2.53)	17.00 (6.86)	11.27 (3.23)	0.001
Platelet recovery day+	12.37 (2.92)	12.48 (3.00)	14.28 (4.23)	43.00 (30.80)	16.64 (8.07)	0.099

TNC – Total Nucleated Cells, SD – Standard Deviation

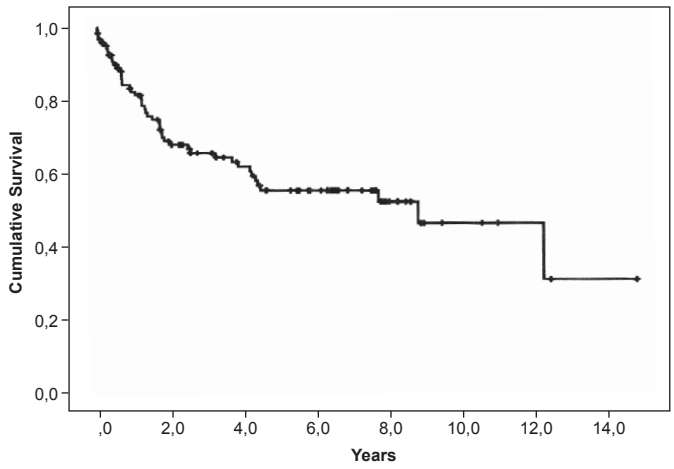


Figure 1 – Overall survival curve of the transplant patients at the HUSM from December 1996 to December 2011.

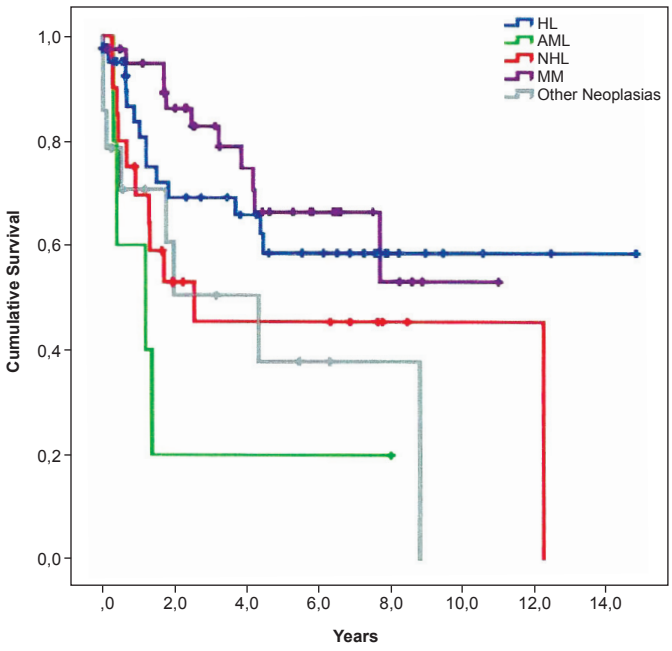


Figure 2 – Overall survival curve by diagnosis of the transplant patients at the HUSM from December 1996 to December 2011.

I – For the group of patients with MM (N=39), the median time to OS was approximately 7.2 years (8-144 months), SD = 0.57. In a year, the OS probability was 94.7%, SD= 0.036; in five years, it was 67.1%, SD= 0.088.

II – For the group of patients with HL (N=43), the median time to OS was approximately 5.57 years (2-180 months), SD = 0.85. In a year, OS probability was 81.6%, SD= 0.063. In five years, it was 55.7%, SD = 0.85.

III – For the group of patients with NHL (N=20), the median time to OS was approximately 2.56 years (3-113 months), SD = 2.26. In a year, it was 69.6%, SD= 0.104. In five years, the probability of survival was 45.5%, SD= 0.121.

IV – For the group of patients with AML (N=5), the median time for OS was approximately 1.2 years (4-108 months), SD= 0.87. In one year, the probability of survival was 60%, SD= 0.219.

V – For the group of patients with other neoplasias (N=13) the median time for OS was approximately 4.36 years (2-83 months), SD= 2.59. In one year, the probability of survival was 61.5%, SD= 0.135. In five years, it was 38.5%, SD= 0.156.

For the OS of transplant patients, no statistically significant differences were found between the diagnoses (P = 0.811) (Figure 2).

DISCUSSION

HSC can reconstitute the bone marrow function after lethal irradiation. This sustained hematopoietic reconstitution after transplantation is referred to as engraftment (6). In PBSCT, the most reliable factor for predicting hematologic recovery is the infused CD34+ cell dose (7).

In this analysis, the median number of CD34+ cells infused in patients after conditioning was $3.17x10^6$/kg. Although $5.0x10^6$kg CD34+ cell dose is ideal in mobilization, there have been reports of successful transplants with a minimum of $1.0x10^6$/kg CD34+ cell dose and many transplant centers perform this procedure successfully with engraftment of $2.0x10^6$/kg CD34+ cell dose (8). According to Kessinger and Sharp (2003), a minimum of $1.0x10^6$/kg CD34+ cell dose is required to ensure hematopoietic recovery after transplantation, with higher doses providing a faster recovery of platelets (9). In their study, Massumoto et al (1996) concluded that CD34+ cells greater than $1.0x10^6$/kg can produce rapid recovery of medullar function (10).

Following the infusion of HSC the median recovery time for neutrophils and platelets was 10 days and 12 days, respectively, which was similar to the time periods found in other studies (11, 12). A correlation was observed between the number of infused CD34+ cells and the time to neutrophil and platelet engraftment, also reported in other studies (7, 13, 14).

Nine patients (9.2%) received a lower dose infusion of CD34+ cells of $2.0x10^6$/kg , ranging from 1.35 to $1.98x10^6$/kg, and in two of them there was delay in the recovery of platelets (32 and 79 days).

Among the transplant patients, three patients did not achieve platelet engraftment, one with AML and two with NHL, with infusions of 2.09, 2.81 and $2.35x10^6$/kg CD34+ cells, respectively, suggesting poor quality of PBSCT, stem cells affected by the use of drugs along the patients treatment or antiviral agents used after infusion (15). Successful engraftment depends not only on the quantity but also on the quality of PBSC mobilized (8).

An important parameter to evaluate the toxicity of transplantation is mortality rate until day +100 post-transplant. Among the 120 transplant patients, death rate was 5%,

which is similar to that described in the literature (16). In a European study with 1482 transplant patients, TMR was 2.8% (17). Castro Jr.et al (2003) reported 9.5% in a group of 21 pediatric patients with different diagnoses (18).

In this study, TMR for MM was 2.5%; Jantunen et al (2006) reported 1.9% and Pallotta et al (2007) described 5%, however, the source of HSC was the bone marrow (17, 19). For HL, it was 2. 3%; Arantes et al (2011) found a 3, 2% TMR in patients with HL and Cortez (2010), 3.74% (20, 21). For the other neoplasias, TMR was 23%, however, as the diagnoses were quite varied, it was not possible to correlate with literature data.

OS of transplant patients was measured from PBSCT to the date of death, regardless of the cause, despite the recurrence of the disease being one of the leading transplantation complications.

Independently from the variables studied during one year, OS probability was 79.8% and 55.1% in five years. This report did not take into account the clinical conditions of patients throughout the process, which limited the comparison with data found in the literature.

In relation to MM, OS probability was 67.1% in five years. Todaro et al (2011) reported a 75% OS after a five year follow-up. The partial or complete response to treatment, prior to transplantation, proved to affect the patient's survival (22). Barlogie et al (2006) reported a survival rate in five years after BMT in MM patients with complete response rates between 42 to 56% (23).

For HL, OS probability in one year was 81.6% similar to that described by Arantes (2011). In five years, it was 55.7% lower than that found by Cortez (2010), who reported 86% (20, 21). International studies described OS rates ranging from 50-80%. In a 2004 study, carried out in Brazil, the OS rate was 44% (24).

In the case of NHL, the rate was 45.5%, similar to that found in the literature, limiting the comparison due to the peculiarities of the subtypes of lymphomas analyzed (25, 26).

In AML, OS probability in one year was 60%, but the number of patients was too small, not allowing comparisons with other studies.

In the group of other neoplasias, OS was 38.5% in five years. PBSCT was considered standard for relapsed germinal tumor; PBSCT in breast cancer patients is still controversial; Ewings sarcoma patients can benefit with the procedure, especially those with lung and bone metastases. There are no benefits for those with brain tumor. PBSCT is a valid strategy for solid tumors, particularly in relapsed diseases; however, there are no randomized phase III clinical trials (RCTs) that could demonstrate the advantages of this type of approach (27).

CONCLUSION

The results of this study suggest that autologous stem cell transplantation, which are done in our institution using peripheral blood stem cell transplant (PBSCT), are similar to others reported in medical literature. The joint efforts of a multiprofessional medical team commited with high quality assistance was essential to meet these results.

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