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A case-control study on cryopreserved *versus* non-cryopreserved strategies for autologous hematopoietic cell transplantation in multiple myeloma

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ABSTRACT

Background: Autologous hematopoietic cell transplantation is a standard treatment for multiple myeloma. The classic practice is with cryopreservation of the peripheral blood stem cells (PBSC) in the period from collection to infusion, but non-cryopreserved storage at 4°C has demonstrated to be feasible and safe. **Methods:** We present a retrospective, case-control study comparing the outcomes in terms of engraftment in two centers in Uruguay, one with cryopreservation (Hospital Británico — HB) and the other with 4°C storage (Hospital Maciel — HM). **Results:** Sixty-nine patients were included during October 15, 2018 and December 23, 2023. Median age was 60 years old (32–72). The median of collected PBSC was 9.0×10^6/kg (range 2.7–32.3), and the median of PBSC infused was 5.4×10^6/kg, (range 2.7–10.8). The time to neutrophil engraftment was 10 days (range 6–12) in HM and nine days (range 7–12) in HB ($p = 0.38$). The time for platelet engraftment was 20 days (range 17–25) in HM and 19 days (range 15–30) in HB ($p = 0.14$). There were no graft failures, and no treatment-related mortality was observed at 100 days. **Conclusions:** Both cryopreserved and non-cryopreserved strategies appear to achieve similar outcomes in terms of engraftment and safety. Non-cryopreservation can be a way to improve affordability and accessibility to autologous hematopoietic cell transplantation in multiple myeloma, particularly in resource-limited areas.

Keywords: Multiple Myeloma. Hematopoietic Stem Cell Transplantation. Cryopreservation. Safety.

INTRODUCTION

Autologous hematopoietic cell transplantation (aHCT) is a standard treatment for many hematologic malignancies, as well as for some solid tumors, and autoimmune diseases. Multiple myeloma[1] (MM) is the main indication for aHCT in adults in Latin America[2] and worldwide.[3] Although the options for the treatment of patients with MM have evolved in the last decades, aHCT is still the preferred choice in the first line

treatment for patients with MM, owing to its favorable impact in terms of progression-free survival or even overall survival in various studies.[4–6]

The standard practice for performing an aHCT included cryopreservation of the cellular product from the collection of the peripheral blood stem cells (PBSC) and their infusion. This process requires special infrastructure and trained personnel and has additional associated costs, which has driven the evaluation of performing aHCT without cryopreservation.[7] Many studies have demonstrated the feasibility of performing aHCT in MM by maintaining the stem cell product at 4°C (range 2–8°C), in a standard blood bank refrigerator for a short period of time, while the patient receives the conditioning regimen and particularly if the storage period does not exceed three days.[8–14]

Improving access to aHCT in MM is of utmost importance, particularly in low- and middle-income countries,[1] and strategies to reduce costs without compromising efficacy and safety should be encouraged. Here we present a study comparing the outcomes in terms of engraftment in two centers in Uruguay, one with cryopreservation and the other one with 4°C storage of PBSC during the conditioning regimen.

METHODS

Study type

This is an observational, descriptive, case-control, retrospective study comparing two strategies for PBSC preservation in aHCT in MM. We analyzed those patients without cryopreservation that were transplanted consecutively at the Hospital Maciel (HM), Montevideo, Uruguay, during the period of the study. They were compared to matched paired controls with cryopreservation that received the aHCT at Hospital Británico (HB), Montevideo, Uruguay, during the same period.

Inclusion criteria

The patients included were over 18 years old; they have been diagnosed with MM; and had received a first aHCT after induction therapy at HM and HB, from October 15th, 2018 to December 23rd, 2023.

Matching criteria

Patients were matched 1:2 (cases/controls). The clinical parameters for matching cases and controls were age, sex, type of MM, stage of the disease, international staging system (ISS) risk score, number of lines of treatment received before transplant, induction regimen, dose of melphalan, mobilization regimen, and number of CD34+ cells collected and infused.

Treatment

Patients in both centers had PBSC collection after mobilization with filgrastim with or without additional use of plerixafor to obtain at least 2×10^6/kg of CD34+ cells at HM and 3×10^6/kg of CD34+ cells at HB by apheresis. The conditioning regimen was melphalan 200 mg/m^2 or reduced to 140 mg/m^2 in patients with co-morbidities. For the patients transplanted at HM, after apheresis collection, the stem cell product was kept at 4°C without cryopreservation. At the HB, the stem cell product was cryopreserved in liquid nitrogen with the cryoprotectant dimethyl sulfoxide (DMSO) at 10% and thawed immediately before infusion.

Definitions

Neutrophil recovery was defined as the first of three successive days with an absolute neutrophil count (ANC) of ≥ 500/µL after post-transplantation nadir. Platelet recovery was defined as the first of three consecutive days with a platelet count of 20,000/µL or higher in the absence of platelet transfusion for seven consecutive days. Graft failure was defined as failures to achieve an ANC ≥ 500/µL by day +30 with associated pancytopenia.[15]

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Statistical analysis

Data collection from the database and clinical records of both centers was authorized by the corresponding ethics committees. The data included the characteristics of the patients, their treatments were obtained, and the cases and controls were matched according to the predefined criteria. The outcome measures collected and analyzed consisted of the incidence of graft failure, neutrophil and platelet engraftment time (days), hematological and non-hematological toxicities, number of red blood cells, and platelet transfusions. An Excel spreadsheet was used to compile data and variables and for mathematical calculations. Statistical calculations were performed using Statistical Package for the Social Sciences 21.0 software. Frequencies and measures of central tendency were used to present the data, and parametric tests, χ^2, were used to correlate variables. *p* was considered statistically significant if it was less than or equal 0.05.

Ethical considerations

This study was approved by the ethics committees of the participating centers, HM and HB. The research was carried out according to the criteria established by the Declaration of Helsinki with its modifications.[16]

Study outcomes

The main objective of the study was to determine the differences between cryopreserved *versus* non-cryopreserved PBSC in patients with MM receiving a first upfront aHCT, in terms of neutrophil, and platelet engraftment. Secondary endpoints were to evaluate the incidence of toxicities, requirements of red blood cells, platelets transfusions, and graft failure in both groups.

RESULTS

Patients and transplant characteristics

The study analyzed the outcomes of 69 patients that underwent their first aHCT between October 15, 2018 and December 23, 2023. Twenty-three patients admitted consecutively at the HM were matched with 46 patients treated at HB in that same period. For the total population of both hospitals, 40 patients (58%) were women and 29 (42%) were men. The median age at transplant was 60 years old (range 31–72) (Table 1).

For the total population, including both centers, most of the patients (97.1%) were staged using the Durie-Salmon (DSS) staging system; and 60 (86.9%) of them did not have renal impairment (stage A of DSS). Based on the ISS, 21 patients (30.4%) were stage I, 31 patients (44.9%) were stage II, and 14 patients (20.2%) were stage III. Data were missing to complete ISS staging in three patients (4.3%) (Table 1).

Pre-aHCT response was classified as stringent compete response in three patients (4.3%), complete response in 19 patients (27.5%), very good partial response in 22 patients (31.9%), and partial response in 25 patients (36.2%).

The collection could be completed in one procedure of apheresis in 60 patients (86,9%), while nine patients (13%) needed more than one procedure. The median number of PBSC collected was 9.0×10^6/kg (range 2.7–32.3), and the median number of PBSC infused was 5.4×10^6/kg, (range 2.7–10.8). Most of the patients (62, 89.9%) received a melphalan dose of 200 mg/m^2, and seven patients (10.1%) received 140 mg/m^2, due to renal impairment. No patient required renal replacement therapy (Table 1).

The differences observed in the use of plerixafor (and therefore in the collected cellularity) are attributed to the different strategies used in each center during the study period. In HB, the policy consisted of systematic collection for two procedures (maintaining a cryopreserved fraction for a future transplant), which explains the greater use of plerixafor and the higher CD34+ yields.

Table 1. Baseline demographics and transplant characteristics.

	Non-Cryopreservation	Cryopreservation	*p*-value
	HM = 23	HB = 46	
Sex	M = 10 (43.5%), F = 13 (56.5%)	M = 19 (41.3%), F = 27 (58.7%)	0.74
Age, median (range)	60 (34–72)	60 (31–69)	0.75
	Stage (Durie-Salmon)		0.07
IA	1	3	
IIA	0	4	
IIIA	18	34	
IIIB	3	4	
Missing data	1	1	
	International staging system		0.19
I	7	14	
II	11	20	
III	4	10	
Missing data	1	2	
	Pre-aHCT depth of response		0.78
CR + sCR	8	14	
VGPR	8	14	
PR	7	18	
	Number of lines of therapy before aHCT		0.46
1	16 (69.5%)	33 (71.7%)	
2	3 (13%)	12 (26.1%)	
> 2	4 (17.5%)	1 (2.2%)	
	Conditioning regimen		
Melphalan 200 mg/m2	20 (87%)	42 (91.3%)	
Melphalan 140 mg/m2	3 (13%)	4 (8.7%)	
	Number of apheresis		0.79
1	21 (91.3%)	39 (84.8%)	
2 or more	2 (8.6%)	7 (15.2%)	
Plerixafor	5 (21.7%)	21 (45.7%)	0.001
CD34+ Collected	5.5 × 10(6) (2.70–15.7)	12.3 × 10(6) (4.7–32.3)	0.008
CD34+ Infused	4.9 × 10(6) (2.70–9.32)	5.47 × 10(6) (2.8–10.8)	0.37

HB: Hospital Británico; HM: Hospital Maciel; aHCT: autologous hematopoietic cell transplant; CR: complete response; sCR: stringent complete response; VGPR: very good partial response; PR: partial response. Source: Elaborated by the authors.

Engraftment, transfusion requirements, and toxicities

The time to neutrophil engraftment was 10 days (range 6–12) in HM and nine days (range 7–12) in HB ($p = 0.38$). The time for platelet engraftment was 20 days (range 17–25) in HM and 19 days (range 15–30) in HB ($p = 0.14$). The median number of red blood cell transfusions was 1 (range 0–3) for HM and 1 (range 0–8) for HB. The median number of platelet transfusions was 2 (range 0–14) for HM and 2 (range 0–12) for HB. No patients developed moderate to severe transfusion associated complications.

Forty-seven patients developed febrile neutropenia, 10 patients (43.5%) from HM and 37 (80.4%) from BH ($p = 0.001$). Blood cultures were positive in two patients (8.68%) in HM and in seven patients (15.2%) in HB ($p = 0.005$).

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In the HB group with cryopreserved PBSC and DMSO utilization, seven patients (15.2%) reported mild (common toxicity criteria grade 1 or 2) adverse reactions including flushing, rash, and nausea but no grade 3 or 4 toxicities were recorded. No infusion associated toxicity was reported in the non-cryopreserved group.

The median stay was 21 days (range 18–34) for HM, and 24 days (range 19–41) for HB (p = 0.78). No graft failures were observed in either group (Table 2).

Table 2. Autologous hematopoietic cell transplantation outcomes, non-cryopreservation *versus* cryopreservation.

	Non-cryopreservation HM = 23	Cryopreservation HB = 46	*p*-value
Engraftment and transfusion requirements			
Neutrophil engraftment, days (range)	10 (6–12)	9 (7–12)	0.38
Platelet engraftment, days (range)	20 (17–25)	19 (15–30)	0.14
Graft failure	0	0	N/A
Transfused RBC units, median (range)	0 (0–3)	1 (0–8)	0.01
Transfused PLT units, median (range)	2 (0–14)	2 (0–12)	0.89
Non-hematologic toxicity			
Febrile neutropenia	10 (43.5%)	37 (80.4%)	0.001
Positive blood cultures	2 (8.7%)	7 (15.2%)	0.005
Side effects during infusion	0	7 (15.2%)	0.0001
Patients stay, day (range)	21 (18–34)	24 (19–41)	0.78
100-day TRM	0	0	

HB: Hospital Británico; HM: Hospital Maciel; RBC: red blood cells; PLT: platelet; TRM: 100-day treatment related mortality. Source: Elaborated by the authors.

DISCUSSION

Multiple myeloma is the main indication for aHCT in adults in Latin America and worldwide.[2,3] However, utilization of aHCT for MM in Latin America, Africa, and Asia is still low compared to Europe or the United States of America,[1] emphasizing the importance of developing methodologies to make the procedure more accessible and affordable, while preserving safety and efficacy.

Cryopreservation, typically with the cryoprotective agent DMSO, has been the standard practice to maintain viability after PBSC collection, allowing time for delivery of the conditioning regimen prior to cell infusion. Although it is essential for preserving the viability of the cells during long-term storage, it has been documented that keeping PBSC at 4°C while the patient is receiving the conditioning regimen is safe and can effectively restore hematopoiesis in aHCT,[7–15,17] allowing the practice of aHCT even in centers with no access to cryopreservation. Therefore, studies comparing both strategies are essential to identify the possible advantages and disadvantages of each procedure.

In our case-control study comparing two contemporaneous cohorts, one with cryopreservation (HB) and the other without it (HM), the main parameters of hematologic reconstitution did not show significant differences, with both groups achieving similar time to neutrophil and platelet engraftment. No graft failures were observed, confirming the efficacy of both strategies. Although there were no major complications associated with the infusion of the cryopreserved cells, the absence of DMSO in fresh infusions can avoid the toxicity associated with this cryoprotectant.[17]

Our study documented a lower incidence of neutropenic fever in the non-cryopreservation group, although the differences can be attributed to different antimicrobial prophylaxis strategies in each of the centers, making it difficult to draw conclusions on this finding. However, a lower incidence of febrile neutropenia in the non-cryopreserved group had been previously reported in the study by Sarmiento et al.,[9] making this topic worth exploring in greater depth in future research.

It should be noted that non-cryopreserved aHCT requires greater coordination between the apheresis team, and the clinical unit for the administration of conditioning chemotherapy to minimize storage time. In contrast, cryopreservation allows for the separation in time of PBSC collection from the start of conditioning, thus maintaining viable cells for longer periods of time, which is logistically important, particularly when the apheresis and clinical unit teams operate independently. Cryopreservation is necessary if the plan is not to use the cells within a few days after collection, such as in the case of planned tandem aHCT or the strategy of storing PBSC for deferred aHCT to protect the progenitors from damage induced by antineoplastic treatment.

Other limitation of non-cryopreservation strategies is the impossibility of maintaining cell viability if the transplant must be postponed once the patient has been collected. Additionally, starting the conditioning immediately after collection, while the patient has a higher leukocytosis due to filgrastim mobilization, may increase the risk of metabolic complications.

The main advantages of implementing a non-cryopreserved aHCT program for MM include the lower costs associated with the procedure and storage equipment, fewer working staff requirement in the processing area, and avoiding DMSO-associated toxicities during infusion.

Although non-cryopreservation short-term storage has the disadvantages described above, it may be a particularly important alternative to promote the development of aHCT in MM in areas with limited resources, because of its lower costs, and infrastructure requirements. Facilitating the availability of aHCT is of particular importance in low- and middle-income countries, where the population has limited access to costly MM therapies, such as new drugs, targeted antibodies, bispecific antibodies or CAR T-cells.[18,19]

Non-cryopreservation aHCT may be a particularly interesting option to facilitate the implementation of new aHCT programs in MM, never neglecting safety, efficacy, and quality control requirements.[20–22]

The comparison presented here has several limitations, *i.e.*, it is a retrospective study, the samples were small, and as the two groups were treated at two different hospitals, other variables may be influencing the outcomes, in addition to the strategies used. However, it reaffirms the observations summarized in a meta-analysis[23] and reviewed by experts[24] in the sense that, although both strategies have pros and cons, both have been shown to be safe and effective.

CONCLUSION

For PBSC storage during the conditioning regimen in aHCT for MM, both cryopreserved and non-cryopreserved strategies appear to achieve similar outcomes in terms of engraftment and safety. Non-cryopreservation can improve affordability and accessibility to aHCT in MM, particularly in resource-limited areas.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are available upon request from the corresponding author.

AUTHORS' CONTRIBUTIONS

Substantive scientific and intellectual contributions to the study: Figueroa B, Ferrando M and Galeano S; **Conception and design:** Figueroa B, Ferrando M and Galeano S; **Acquisition of data:** Figueroa B, Perdomo M and Ferrando M; **Analysis and interpretation of data:** Figueroa B, Galeano S, Borelli G, Landoni AI and Muxí P; **Technical procedures:** Figueroa B, Galeano S, Riva E, Vázquez A, Oliver C, Pierri S, De Giuda R and Urrutia R; **Statistics analysis:** Martinez L, Isern M, Martínez C, Otero C, Figueroa B, Galeano S, Oliver C, Muxí P, Remedi V and Mori M; **Manuscript preparation:** Galeano S, Figueroa B, López E, Guidali C, Gai R, Marcalain V,

Bello L, Moraes V, Viano L, Olivera A, Lamela C, Ambrosini C, Pisano S, Prieto J, Gabús R, Landoni AI and Muxí P; **Manuscript writing:** Galeano S, Figueroa B, Irigoin V, Borelli G, Riva E, Ferrando M, Oliver C, Landoni AI, Pierri S and Muxí P; **Final approval:** Galeano S and Figueroa B.

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