Efficacy and safety of autologous transplant with non-cryopreserved peripheral blood stem cells in myeloma and lymphoma in Algeria. 10 years' experience

Efficacité et sécurité de l'autogreffe avec des cellules souches non cryopréservées au cours du myélome multiple et des lymphomes en Algérie. Expérience de dix

Mohamed Amine Bekadja, Badra Entasoltan, Kamila Amani, Hafida Ouldjeriouat, Soufi Osmani, Samira Bouchama, Leila Charef, Abdessamed Arabi, Mohamed Brahimi, Amar Rachid Bouhass, Nabil Yafour

Department of Hematology and Cell Therapy, Etablissement Hospitalier Universitaire (EHU) 1st November, Oran, Ahmed Benbella 1 University, Oran, Algeria

Abstract

Introduction : La conservation des cellules souches périphériques, dans des réfrigérateurs standards à +4°C, est une alternative simple et peu coûteuse à la cryoconservation pour la plupart des patients vivant dans des pays aux ressources limitées. Nous présentons l'expérience de 10 années de notre service d'hématologie d'Oran en Algérie utilisant des cellules souches non cryo préservées après un conditionnement avec de hautes doses de chimiothérapie, dans une importante cohorte de patients atteints de myélome multiple et de lymphomes.

Méthodes: De mai 2009 à décembre 2019, des greffes autologues de cellules souches (ASCT) ont été réalisées dans notre centre, dont 420 au cours du myélome multiple (MM) et 154 au cours des lymphomes. La source du greffon chez tous les patients consistait en cellules souches périphériques autologues obtenues après mobilisation avec un facteur de croissance cellulaire
(G-CSF) et cytaphérèse. Le nombre médian de cytaphérèse était de 1 (1-3) et le greffon cellulaire a été conservé dans le réfrigérateur de la banque de sang à +4°C, dans des packs de transfert de 300 ml (Baxter Healthcare) composés de gaz imperméable et de chlorure de polyvinyle. La viabilité des cellules souches recueillies est évaluée par cytométrie en flux à l'aide de 7'AAD (7 Amino-Actinomycine D) et a été déterminée par un test d'exclusion
au colorant bleu trypan. Le régime de conditionnement de chimiothérapie (Melphalan 200 ou 140, BEAM, CBV, EAM, BeEAM) a commencé une fois qu'un minimum de 2×106 cellules CD34+/kg dans le MM ou 3x106 cellules CD34+/kg dans le lymphome a été obtenu.

Résultats: Chez les patients atteints de MM, l'âge médian à la greffe était de 54 ans (Extrêmes ; 27-73). Le nombre médian de cellules CD34+ recueillies était de 3,2x106/kg (extrêmes : 1, 22 à 13, 22) et la viabilité dans tous les cas était supérieure à 90%. Tous les patients avaient une prise de greffe avec une durée médiane de 9 jours pour les PNN (intervalle ; 7 à 24 jours) et une indépendance plaquettaire en médiane à J13 post autogreffe (intervalle ; 9 à 39 jours). Il n'y a pas eu d'échec de prise de greffe. La mortalité liée à la greffe à J100 était de 3,5 %. La réponse globale à la greffe a été de 99 % (rémission complète (RC)=64,5 % ; très bonne réponse partielle (TBRP)=34 %, réponse partielle (RP)=1,5%). La survie globale (SG) estimée à 5 ans était de 68 % et la médiane de survie sans progression (SSP) post-greffe était de 47 mois. Au 31 décembre 2021 (date de point), 41% des patients ont rechuté, 28% sont décédés après progression de la maladie et 305 (75%) patients sont vivants dont 237 (59%) sans activité de la maladie après un suivi médian de 52 mois (extrêmes ; 13 à 149). Chez les patients atteints de lymphome, 98 lymphomes de Hodgkin (LH) et 56 lymphomes non hodgkiniens (LNH) ont subi une autogreffe. L'âge médian à la greffe était de 28 ans (extrêmes : 16-55) et 33 ans (17-61) respectivement. Après mobilisation, une médiane de 4,25x106/kg (NHL) et 4,14x106/kg (HL) de CD34+ ont été perfusées et la viabilité médiane des cellules souches après une conservation de 7 jours au réfrigérateur était de 82%. Le temps médian pour atteindre 0,5 G/L de neutrophiles ou plus était de 14 jours (9-44) et de 15 jours (11-27) dans le LH et le LNH, le temps médian pour atteindre plus de 20 G/L de plaquettes était de 16 jours (10-37) et 17 jours (15-28) pour le HL et le NHL.
La SG à 5 ans était respectivement de 76% et 67% pour les patients atteints de LH et de LNH. La mortalité liée à la greffe à J100 était de 5% dans le LH et de 12,5% dans le LNH.

Conclusion: Cette étude montre la faisabilité d'une thérapie intensive suivie d'une autogreffe de cellules souches non cryo-préservées chez les patients atteints de MM et de lymphome. Cette technique est peu coûteuse, efficace, sécurisée et peut potentiellement permettre l'utilisation généralisée des activités d'autogreffe de cellules dans d'autres centres d'hématologie en Algérie et dans les pays aux ressources limitées.

Mots clés : Myélome multiple; lymphome; autogreffe ; cellules souches périphériques; non-cryo-préservation; autologue.

Résumé

Introduction: The storage of harvested stem cells, in standard refrigerators at +4°C, is a simple and inexpensive alternative to cryopreservation for most patients living in countries with limited resources. We present the 10 years' experience of our single center from Oran in Algeria using non-cryopreserved stem cells after conditioning with high dose chemotherapy, in a large group of myeloma and lymphoma patients.

Methods: From May 2009 to December 2019, autologous stem cell transplantation (ASCT) was carried out in our center, of which 420 with multiple myeloma (MM) and 154 patients with lymphoma. The source of stem cells in all patients consisted of mobilized autologous peripheral blood stem cells (PBSCs). A median of one cytapherisis was performed (range, 1-3) and the products of the aphaeresis were stored in a conventional blood bank refrigerator at +4°C, in 300-mL transfer packs (Baxter Healthcare) composed of impermeable gas, polyvinyl chloride plastic film. The viability of the harvested cells is assessed by flow cytometry using 7'AAD (7 Amino-Actinomycine D) and was determined by a trypan blue dye exclusion test. The chemotherapy conditioning regimen (Mel200, BEAM, CBV, EAM, BeEAM) started once a minimum of 2×106 CD34+cell/kg in MM or 3x106 CD34+cell/kg in lymphoma was obtained.

Results: In MM patients, the median age at ASCT was 54 years (range; 27-73). The median harvested CD34+ cell count was 3,2x106/kg (range; 1, 22 to 13, 22) and the viability in all cases being >90%. All patients had engraftment on the median of day 9 (range; 7 to 24) and platelet transfusion independence on the median of day 13 (range; 9 to 39). There was no graft failure. Transplant related mortality (TRM) at 100 days was 3,5%. The overall response to transplant was 99% (complete remission (CR) =64,5%; very good partial remission (VGPR) =34%, partial remission (PR) =1,5%). The estimated overall survival (OS) at 5 years was 68% and the median post-transplant progression-free survival (PFS) was 47 months. On December 31th 2021, 41% patient relapsed and 28% died after disease progression. 305 (75%) patients are alive and 237 (59%) without disease activity after a median follow-up of 52 months (range; 13 to 149). In lymphoma patients, 98 Hodgkin`s lymphoma (HL) and 56 non-Hodgkin´s lymphoma (NHL), were auto grafted. The median age at ASCT was 28 years (range; 16-55) and 33 years (17-61) respectively. After mobilization a median of 4,25x106/kg (NHL) and 4,14x106/kg (HL) of CD34+ was infused and the median viability of the cells after 7 days of refrigeration (trypan blue exclusion) was 82%. The median time to achieve 0,5 G/L neutrophil or more was 14 days (9-44) and 15 days (11-27) in HL and NHL, median time to achieve 20 G/L platelets or more at a median of 16 days (10-37) and 17 days (15-28) in HL and NHL. The OS at 5 years was 76% and 67% for patients with HL and NHL respectively. Transplant related mortality at 100 days was 5% in HL and 12,5% in NHL.

Conclusion: This study demonstrates the feasibility of intensified therapy followed by autologous non-cryopreserved PBSCs infusion in MM and lymphoma patients. This method of ASCT is cheaper, and may potentially enable the widespread use of ASCT activities in other hematology centers in Algeria and in developing countries.

Keywords: autologous, stem cell, non-cryopreserved, myeloma, lymphoma

Correspondance

Professor Mohamed Amine Bekadja
Department of Hematology and Cell Therapy EHU 1st November, Oran, Algeria Ahmed Benbella 1 University, Oran, Algeria
E-mail: mabekadja@yahoo.fr

LA TUNISIE MEDICALE - 2022 ; Vol 100 (11) : 762 - 768

INTRODUCTION

Autologous stem cell transplantation (ASCT) after a high dose chemotherapy conditioning is an established treatment modality with definitive indications for many hematological disorders. However, this treatment procedure requires many expensive resources, such as freezing of the harvest product in order to maintain cell viability until stem-cell reinfusion.

The storage of harvested stem cells, in standard refrigerators at +4°C, is a simple and inexpensive alternative to cryopreservation for most patients living in countries with limited resources (1). In 2007, Wannesson et al. published a systematic review in which they demonstrated the feasibility and the safety of ASCT without cryopreservation of the graft (2).

We present the first experience of our single center from Oran in Algeria using refrigerated, non-cryopreserved stem cells after conditioning with high dose chemotherapy, in a large group of myeloma and lymphoma patients.

METHODS

In May 2009 we started to perform ASCT without freezing of the harvested bags. From May 2009 to December 2019, 574 ASCT were carried out in our center, of which 420 were for patients less than 65 years old, presenting with multiple myeloma (MM) but a few patients over the age of 65 years have undergone autograft. In154 patients with lymphoma, ASCT is indicated as first-line treatment, in the mantle cell lymphoma, and all patients were in CR before ASCT after a salvage therapy during relapsed or refractory forms of Hodgkin's diseases (HL) or non-Hodgkin lymphomas (NHL).

Mobilization

The source of stem cells in all patients consisted of mobilized autologous peripheral blood stem cells (PBSCs). For mobilization of PBSCs, patients received granulocyte colony stimulating growth factor (G-CSF) at a dose of 15 mcg/kg subcutaneously once daily for 5 days (3-4).

Apheresis

Cytapheresis was performed on days -2 and -1. A volume of 8-10 L of blood was processed in each sitting, using the aphaeresis machine OPTIA® (Cobe, Spectra). One or two cytapheresis were performed twelve hours after the fourth injection, the number of CD34+cells was assessed immediately after the end of the cytapheresis and if a minimumnumber of 2×10^6 CD34+cells/kg is not reached another cytapheresis was performed the next morning. A median of one cytapheresis was performed (range, 1-3). Cytapheresis was done from the femoral vein in all patients using a dialysis catheter. A sample of the stem cell harvest was obtained and total cell counts were determined using an automated cell counter; the differential cell count was done manually. For CD34+ counts, cells were labeled with fluorescein-conjugated anti-CD34+ and analyzed using a FACS scan flow cytometer to yield an absolute CD34+ count (5).

Conservation

The products of the aphaeresis and 1-mL aliquots were kept in ACD-A (Baxter Healthcare, Deerfield, IL) and stored in a conventional blood bank refrigerator at +4°C, in 300-mL transfer packs (Baxter Healthcare) composed of impermeable gas, polyvinyl chloride plastic film [6].

Viability

Viability of the harvested cells is assessed by flow cytometry using 7'AAD (7 Amino-Actinomycine D) until there injection of the harvests. The viability of cells was determined by atrypan blue dye exclusion test (6).

Conditioning Regimen

The chemotherapy conditioning regimen started once a minimum of 2×10^6 CD34+cell/kg in MM or $3x10^6$ CD34+cell/kg in lymphoma were obtained. In case of a myeloma patient, the MEL200 (Melphalan 200 mg/m2) is used in 318 patients and Melphalan 140 mg/m^2 in 102 patients. In lymphoma patient (HL or NHL), the conditioning regimen were CBV (7) in 15 patients, a 3 days schedule: Cyclophosphamide 60 mg/kg day-3 and day-2, BCNU: 400 mg/m^2 day-3 and VP16 700 mg/m^2 day-3, day-2 andday-1), 64 patients with standard BEAM (7) regimen (BCNU: 300 mg/m^2 at day-2, VP16: 200 mg/m^{2}at day-5 to day-2, Cytarabine: 400 mg/m^2 at day-5 to day-2, Melphalan: 140 mg/m^{2}at day-1), and in case of unavailability of BCNU we used EAM (8) protocol which is an even more intensive schedule in 63 patients (VP16: 200 mg/m^2 at day-5 to day-2, Cytarabine: 2000 mg/m^{2}at day-5 to day-2, Melphalan: 140 mg/m^2 at day-1). We used also Bendamustine-EAM (9), (150 mg/m^{2}in day-7 and day-6 and EAM, in case of unavailability of BCNU) in 12 patients. Stem cells were reinfused intravenously to the patient on day 0. To do this, stem cells were removed from the conventional blood bank refrigerator and thawed at room temperature. All patients received prophylactic ciprofloxacin (250 mg twice daily), acyclovir (500 mg/day) and fluconazole (200 mg twice daily). Antibiotics were used until granulocytes

were greater than 0.5 G/L. Patients received subcutaneous G-CSF (5µg/kg/day) from day +1 of ASCT until neutrophil engraftment (>0.5G/L) in lymphoma. Platelet transfusions were given if platelet counts were below 20 G/L without risk factors for bleeding. Reed Blood cells (RBC) were given to patients with anemia-related symptoms or hemoglobin values below 8 g/dl. Blood products transfused during the post-transplant period were irradiated with 25 Gy.

Engraftment

Engraftment was calculated from day 0 of the stem cell transplant. Neutrophil engraftment required a sustained absolute neutrophil count of 0,5 G/L for 3 consecutive days. Engraftment of platelets required a platelet count of 20 G/L (un-transfused), with no platelet transfusions within the preceding 48 hours. Evaluation of response to transplantation was assessed on day 100 post-transplant.

Statistics

Overall survival (OS) was defined as the time from date of transplant until death or date of censor. Progression free survival (PFS) was evaluated in all patients who have achieved a complete response (CR) or very-good partial response (VGPR) after transplantation. It was calculated from the CR or VGPR to relapse or death. The Kaplan-Meier method was used to assess survival. The data were censored on December 31th 2021.

RESULTS

From May 2009 to December 31th 2019, we performed 574 ASCT without cryopreservation of the graft in our center in Oran, 420 patients with MM and 154 patients with lymphoma. In MM patients, the median age at ASCT was 54 years (range; 27-73). There were 254 males and 166 females. Durie Salmon status was as follows: 335 IIIA, 55 IIIB and ISS I: 61(25%), ISS II: 67 (28%), ISS III: 112 (47%). The induction treatment before ASCT was VAD (n=51, %), VD (n=64, %), VCD (n=105, %) or VTD (n=160, %) and others (n=39 (%). Evaluation response before ASCT showed 122 (29%) in CR 199 (47%) in VGPR, 67 (16%) in PR and 32 (8%) in progression (Table 1). After 24 hours of refrigeration, the median harvested CD34+ cell count was $3,2x10^6$/kg (range; 1, 22 to 13, 22) and the viability in all cases being over 90%. All patients had engraftment on the median of day 9 (range; 7 to 24) and platelet transfusion independence on the median of day 13 (range; 9 to 39). There was no graft failure. Grade 4 hematological toxicity was observed in all patients. Mucositis was seen in 68% of patients, grade 3 mucositis was observed in 63 patients (15%) and grade 3 infections were observed in 84 patients (20%). Patients received a median of 2 units (range, 0–8) platelet transfusions and a median of 2 units (range, 0–9) RBC transfusions during hospital stay. Transplant related mortality (TRM) at 100 days was 3.57% (n=15). The overall response to transplant was 99% (CR=261; 64,5%-VGPR=138; 34%-RP=6; 1,5%). Among the 405 evaluable patients, the median post-transplant OS was 117 months (range; 104,43 to 129,56) (Table 2). The estimated OS at 5 years was 68% (Figure 1) and the median post-transplant PFS was 47 months (range; 40, 21 to 53,78) (Figure 1). At the December 31th 2021, 167 (41%) patient relapsed and 115 (28, 39%) died after disease progression. 305 (75, 30%) patients are alive and 237 (59%) without disease activity after a median follow-up of 52 months (range; 1 to 149).

Table 1. Patient characteristics at diagnosis in multiple myeloma patients.

MM (n= 420 patients)	N	%
Age (median, range)	54 (27-73)	-
Gender (Male/Female)	254/166	Sr=1,53
Performans status :		
▪ 0-1	255	61
▪ ≥2	144	34
▪ NA	21	5
Durie Salmon classiffcation		
▪ IIIA	335	78
▪ IIIB	55	13
Monoclonal component :		
▪ IgG	228	54,5
▪ IgA	69	16,5
▪ Light Chain	80	19
▪ NA	43	10
ISS score : (evaluable n=240)		
▪ ISS 1	61	25
▪ ISS 2	67	28
▪ ISS 3	112	47
▪ NA	180	43
Induction protocol:		
▪ VAD	51	12
▪ VD	64	15
▪ VCD	105	25
▪ VTD	160	38
▪ Others	40	10
Length between diagnosis-ASCT (months)	9 (6-86)	-
Disease status before ASCT		
▪ CR	122	29
▪ VGPR	199	47
▪ PR	67	16
▪ Refractory	32	8

MM: multiple myeloma; NA: not available; ASCT: autologous stem cell transplant; CR: complete response; VGPR: very good partial response; ISS: International scoring system;

Table 2. Patient characteristics at diagnosis in Hodgkin lymphoma and Non-Hodgkin lymphoma.

N=154 patients	HL(n=98)	NHL(n=56 pts)
Age (median, range)	28 (16-55)	33 (17-61)
Gender (Male/Female)	54/44	30/26
Performans status :		
▪ 0-1	61 (62.5%)	44 (79%)
▪ ≥2	9 (9%)	7 (12%)
▪ NA	28 (28.5%)	5 (9%)
Ann Arborclassiffcation		
▪ I-II	10 (10.20%)	-
▪ III-IV	86 (87.75%)	-
▪ NA	2 (2.05%)	-
Sub-type lymphoma		
▪ DLBCL B	-	40 (71.4%)
▪ DLBCL T	-	09 (16.07%)
▪ MCL	-	04 (7.14%)
▪ NK-T Lymphoma	-	02 (3.57%)
IPS score :		
▪ IPI≥ 2	-	34 (61%)
▪ MIPI≥3	-	3 (75%)
Induction protocol:		
▪ ABVD	51 (53%)	-
▪ BEACOPP	20 (20.4%)	-
▪ CHOP	-	4 (7.14%)
▪ CHOEP	-	5 (8.92%)
▪ R-CHOP	-	39 (69.64%)
▪ R-DHAP	-	4 (7.14%)
▪ Others	27 (27.5%)	3 (5.37%)
Length between diagnosis-ASCT (months)		10 (8-86)
Disease status before ASCT		
▪ CR	56 (57%)	38 (68%)
▪ PR	15 (15.3%)	8 (14%)
▪ Refractory	4 (4.08%)	5 (9%)
▪ NA	23 (23.46%)	5 (9%)

DLBCL B: diffuse large B cell lymphoma B or T; MCL= Mantle cell lymphoma, NK-T: natural killer T lymphoma; IPS: International prognostic Index; Mantle IPI; ASCT: autologous stem cell transplant; CR: complete response; VGPR: very good partial response; NA: not available.

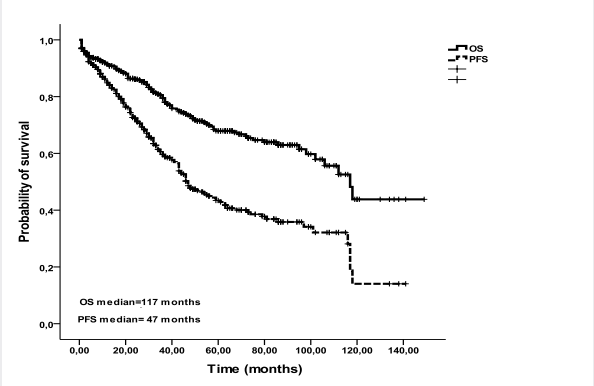

Figure 1. Overall survival and Progression free survival in MM patients.

In lymphoma patients, 98 HL and 56 NHL were autografted. The median age at ASCT was 28 years (range; 16-55) and 33 years (17-61) respectively. After mobilization with G-CSF only, 15 µ/kg/day for 5 days, a median of $4,25x10^6$/kg (NHL) and $4,14x10^6$/kg (HL) of CD34+ was infused and the median viability of the cells after 5-7 days of refrigeration (trypan blue exclusion) was 82%. The median time to achieve 0,5 G/L neutrophil or more was 14 days (9-44) and 15 days (11-27) in HL and NHL, median time to achieve 20 G/L platelets or more at a median of 16 days (10-37) and 17 days (15-28) in HL and NHL. The OS at 5 years was 76% and 67% for patients with HL (Figure: 2) and NHL (Figure: 3) respectively. The PFS at 5 years was 69% and 67% in HL and NHL respectively. Transplant related mortality at 100 days was 5% in HL and 12,5 in NHL. At the December 31th 2021, 11 (12%) patient relapsed and 24 (25%) died after disease progression and 74 (76%) patients are alive in HL after a median follow-up of 87 months (range; 10 to 151). In NHL, 2 (4%) patients relapsed, and 18 (32%) died after disease progression and 38 (68%) are alive after a median follow-up of 66 months (24-129). Grade 4 hematological toxicity was observed in all patients. Grade 3 mucositis was observed in 76 patients (49%) and grade 3 infections were observed in 57 patients (37%). Patients received a median of 3.5 units (range, 0–10) platelet transfusions and a median of 3 units (range, 0–12) RBC transfusions during hospital stay.

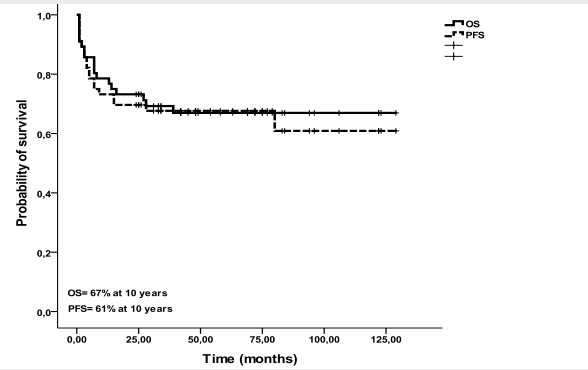

Figure 2. Overall survival and Progression free survival of non Hodgkin's lymhoma.

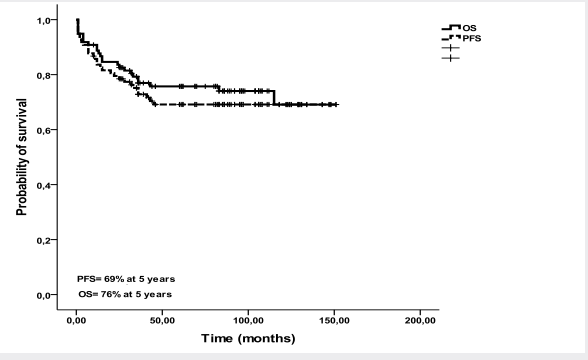

Figure 3. Overall survival and Progression free survival of Hodgkin's lymphoma patients.

DISCUSSION

This study demonstrates the feasibility of intensified therapy followed by autologous non-cryopreserved PBSCs infusion in MM and lymphoma patients. This method of ASCT is cheaper, and may potentially enable the widespread use of ASCT activities in other hematology centers in Algeria and in developing countries.

The number of publications regarding non-cryopreserved autologous transplant is scarce because of the widespread use of the cryopreserved stem cells (10). Among 21 hematology centers in Algeria, only two centers can offer ASCT to MM patients and lymphoma (11). The EHU 1st November in Oran is the second center and our ASCT program started in May 2009 and has implemented the practice of keeping the stem cells in a conventional blood bank refrigerator. The advantages of this technique lie in the fact that it "avoids" the use of cryopreservation, an expensive process that requires special equipment as well as liquid nitrogen for freezing to –180°, the consumables, albumin and dimethyl sulfoxide (DMSO) (fluid retention CSH) (12). Moreover, the simple preservation of PBSCs in a blood bank refrigerator at +4°C until re-infusion into the patient is devoid of any toxic side effects that are described with DMSO (13). This technique has also the advantage of reducing the time between the last induction chemotherapy and ASCT. The only constraint to this method is the need for a rigorous organization of scheduling patients on this protocol.

The results of our study in MM patients show similar results of satisfactory engraftment with a median time to neutrophil recovery of 10 days (range 6-17) and median time to platelet transfusion independence of 13 days (range, 9-24) (14-16). Also, results of our study in lymphoma patients are acceptable and clearly superior to those obtained with conventional chemotherapy in the same institution (17-18). A comparability study with cryopreserved cells from the EBMT group showed a slightly longer duration of aplasia with non-frozen cells but identical TRM rates and survival (19). We have been able to reproduce the results obtained by autografting MM and lymphoma patients in more advanced countries (20-24) and, as a result, to offer this therapeutic option to patients living in Algeria who could not afford the cost of a conventional autografting procedure. In this study, we have shown that ASCT can be kept at +4ºC in a conventional blood bank refrigerator for up to seven days and use them to rescue high-dose chemotherapy in both MM and lymphoma patients. Avoiding freezing procedures results in substantial cost savings. The availability of freezing devices for hematopoietic stem cells is not anymore an obstacle to start an autologous transplantation program. This observation is critical in areas of underprivileged economic circumstances, where more than 50% of the inhabitants of the world live. Using this approach, the cost of ASCT in our country is expected to be substantially lowerthan that reported in Europe (25-26). This cost saving procedure is critical in developing countries. These data are to be taken into account when considering treatment options in MM and lymphoma patients, mainly in developing countries.

CONCLUSION

We can conclude that ASCT with non-cryopreserved grafts is feasible and safe even with long time regiments such as BEAM or EAM or Be-EAM. The harvested cells can be kept in the refrigerator for until their reinfusion. However the lake of freezing possibilities requires an efficient coordination of stem-cell mobilization, apheresis, administration of the high-dose therapy and the stem-cell reinfusion that may be more flexible in centers that use cryopreservation.

Table 3. Engraftment parameters after high-dose chemotherapy and ASCT in patients with MM.

MM (n=420)	
Median cytapheresis	1 (1-2)
Median CD34+ (x10^6/kg)	3.2 (1.22-13.22)
Median viability	94% (89%-97%
Conditioning regimen: ▪ Mel 200 ▪ Mel 140	 318 102
ANC ≥ 0,5 G/L (median, range)	9 (4-27)
Platelets count≥ 20 G/L (median, range)	13 (9-39)
Mucositis (rate)	68%
TRM (median, ranfe)	3.57% (n=15)
RBC (median, range)	2 (0-9)
Platelets (median, range)	2 (0-8)
Disease post ASCT (n=405 evaluable) ▪ CR ▪ VGPR ▪ PR	261 (64.5%) 138 (34%) 6 (1.5%)

ASCT = autologous stem cell transplantation; MM= multiple myeloma; Mel 200= melphalan 200 mg/m2; Mel 140= melphalan 140 mg/m2; ANC= Absolut neutrophil count; TRM= treatment related mortality; RBC= red blood cell.

Table 4. Engraftment parameters after high-dose chemotherapy and ASCT in patients with HL-NHL.

	HL (n=98)	NHL (n=
Median cytapheresis	2 (1-4)	2 (1-3)
Median CD34+ (x10^6/kg)	4.14 (1.41-21.05)	4.25 (1.97-9.53)
Median viability	84.4 (74-89)	
Conditioning regimen:		
▪ CBV	15	-
▪ BEAM	45	19
▪ BeEAM	05	07
▪ EAM	33	30
ANC ≥ 0,5 G/L (median, range)	14 (9-39)	15 (8-31)
Platelets count≥ 20 G/L (median, range)	17 (11-44)	17 (15-28)
Mucositis (rate)	74%	78%
TRM (median, ranfe)	5.1% (n=5)	12.5% (n=7)
RBC (median, range)	3 (0-12)	3 (0-7)
Platelets (median, range)	3 (0-10)	3.5 (1-8)
Disease status post ASCT		
▪ CR	84 (90%)	44(90%)
▪ PR	1(1%)	3 (6%)
▪ Relapse	8 (9%)	2 (4%)

ASCT= autologous stem cell transplant; HL= Hodgkin lymphoma; NHL= Non-Hodgkin lymphoma; ANC= Absolut neutrophil count; TRM= treatment related mortality; RBC= red blood cell; CR= complete response; PR= partial response.

REFERENCES

1. Ruiz-Argüelles Gj. Stem Cell Transplantation Procedures Are Becoming Affordable For Individuals Living In Developing (Middle Income) Countries.ActaHaematol. 2016; 135 (2): 79-80.
2. Wannesson L, Panzarella T, Mikhael J, Keating A. Feasibility and safety of autotransplants with non-cryopreserved marrow or peripheral blood stem cells: a systematic review. Ann Oncol. 2007, 8: 623–632.
3. Talhi S, Osmani S, Brahimi M, Yafour N, Bouhass R, Arabi A et Al. The use of granulocyte colony stimulating factor (g-CSF) (filgrastim) alone in the mobilization of stem cell in the autologous stem cell transplantation. Transfus Apher Sci. 2013 Aug; 49 (1):97-9.
4. Yafour N, Brahimi M, Osmani S, Arabi A, Bouhass RA, Bekadja MA. Biosimilar G-CSF (filgrastim) is effective for peripheral blood stem cell mobilization and non-cryopreserved autologous transplantation. Transfusion Clinique et Biologique. 2013, 20 :502–504.
5. Papadimitriou, C.A., Dimopoulos, M.A., Kouvelis, V. Non-cryopreserved peripheral blood progenitor cells collected by a single very large-volume leukapheresis : a simplified and effective procedure for support of high-dose chemotherapy. J ClinApher, 2000,15(4): 236- 241.
6. Brahimi M, Osmani S, Yafour N, Bekadja S, Bekadja MA. Viability and functionality of non-cryopreservedperipheral stem cellgraftsat + 4°C. Revue Algérienne d'hématologie, 2011, 5: 46-48 (www.sahts-dz.com).
7. Puig N, De La Rubia J, RemigiaMj et Al. Morbidity and transplant-related mortality of CBV and BEAM preparative regimens for patients with lymphoid malignancies undergoing autologous stem-cell transplantation. Leukemia Lymphom. 2006; 47: 1488-94.
8. Bekadja MA. EAM as a new conditioning regimen for lymphoma patients undergoing autologous stem cell transplant. J Blood Lymph, 2014, 4 :e115.
9. Chantepie S, Tchernonog E, Peyrade F, Larcher MV, Diouf M, Fornecker LM, et Al. Bendamustine-based (BeEAM) conditioning before autologous stem cell transplantation: result of a French multicenter study of 386 patients from LYSA centers. Blood 2016, 128:3450.
10. Bekadja MA, Bouhass R. Non-cryopreserved peripheral stem cell (PCS) autograft for multiple myeloma and lymphoma in developing countries. Int J Hematology And Therap, 2015, 1(1): 1-6.
11. Bekadja MA, Brahimi M, Osmani S, Yafour N, Krim A, Serradj F, et al. Hematopoietic stem cell transplantation in Algeria. Hematol Oncol Stem Cell Ther. 2017, (17) 30057-2.
12. Gonzalez-Lopez Tj, Sanchez-Guijo Fm, Ortin A, Crusoe E, Cordoba I, Corral M, et al. Ischemic stroke associated with the infusion of DMSO-cryopreserved auto-PBSC. Bone Marrow Transplantation 2010; 1-2.
13. AlessandrinoEp, P Bernasconi P, Colombo A, Caldera D, Martinelli G, Vitulo P, et al. Pulmonary toxicity following carmustine-based preparative regimens and autologous peripheral blood progenitor cell transplantation in hematological malignancies. Bone Marrow Transplantation (2000) 25, 309–313.
14. Bekadja MA, Brahimi M, Osmani S, Arabi A, Bouhass R, et al. A simplified method for autologous stem cell transplantation in multiple myeloma. HematolOncol Stem Cell Ther, 2012, 5: 49-53.
15. Kayal, S., Sharma, A., Iqbal, S., et al. High-dose chemotherapy and autologous stem cell transplantation in multiple myeloma: a single institution experience at all India institute of medical sciences, New Delhi, using non-cryopreserved peripheral blood stem cells. Clinical Lymphoma,Myeloma& Leukemia, 2014, 14(2): 140-147.
16. Bekadja MA, Brahimi M, Osmani S, Talhi S, Amani K, Ouldjeriouat H. Non- cryopreserved hematopoietic stem cell transplantation in multiple myeloma. A single center experience in Oran (Algeria). Blood, 2015,126:1990.
17. Mabed, M., Shamaa, S. High-dose chemotherapy plus non-cryopreserved autologous peripheral blood stem cell transplantation rescue for patients with refractory or relapsed Hodgkin disease. Biology of Blood and Marrow Transplantation, 2006, 12(9): 942-948
18. Karduss-Urueta Aj, Druiz-Arguelles Gj, Frcp (Glasg), Perez R, Ruiz-Delgado Gj, Cardona Am, et al. Cell-Freezing devices are not strictly needed to start an autologous hematopoietic transplantation program: Non-cryopreserved peripheral blood stem cells can be used to restore hematopoiesis after high dose chemotherapy: A multicenter experience in 268 autografts in patients with Multiple Myeloma or Lymphoma. Study on behalf of the Latin- American Bone Marrow Transplantation Group (LABMT). Blood, 2014, 124: 849.
19. Bekadja MA, Boumendil A, Blaise D, Patrice Chevallier P, Karl S Peggs K S, Salles G et al. Non-cryopreserved hematopoietic stem cells in autograft patients with lymphoma: a matched-pair analysis comparing a single

center experience with the use of cryopreserved stem cells reported to the European Society for Blood and Marrow Transplantation registry. Cytotherapy. 2021, 23 (6): 483-487.

20. Sierra J, Conde E, Iriondo A, Brunet S, Marin J, Perez De Oteiza J et al. Frozen vs non frozen bone marrow for autologous transplantation in lymphomas: a report from the Spanish GEL/TAMO cooperative group.Ann Hematol 1993; 67: 111–114.
21. Carella, A.M., Bellei, M., Brice, P., et al. High-dose therapy and autologous stem cell transplantation versus conventional therapy for patients with advanced Hodgkin's lymphoma responding to front-line therapy: long-term results. (2009) Haematologica 94 (1): 146-148.
22. Van Den Neste, E., Casasnovas, O., Andre, M., et al. Classical Hodgkin's lymphoma: the Lymphoma Study Association guidelines for relapsed and refractory adult patients eligible for transplant. (2013) Haematologica 98(8): 1185-1195.
23. Ferme C, Mounier N, Divine M Et Al. Intensive salvage chemotherapy with high-dose chemotherapy for patients with advanced Hodgkin in relapse or failure after initial chemotherapy: results of the GELA h89 trial. J Clin Oncol, 2002, 20:467-475.
24. Cook G, Williams C, Brown JM, et al. High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial. 2014, The lancet oncology 15(8): 874-885.
25. Faucher C, Le Corroller Soriano Ag, Esterni B, Vey N, Stoppa Am, Chabannon C, et al. Randomized study of early hospital discharge following autologous blood SCT: medical outcomes and hospital costs. Bone Marrow Transplant. 2011; Jul 4.
26. Clemmons Ab, Anderegg S. Mixed outpatient-inpatient autologous stem cell transplant for multiple myeloma: a cost-saving initiative in a resource constrained environment. J Oncol Pharm Pract. 2017; 23(5):384-388.