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Non-Cryopreserved Peripheral Stem Cell (pscs) Autograft for Multiple Myeloma and Lymphoma in Developing Countries

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Abstract

Autologous peripheral blood progenitor cell (PBPC) transplant is a standard indication in the multiple myeloma (MM) and lymphoma. The use of non-cryopreserved PBPCs is not usual despite its safety, feasibility and efficacy. Few data exists in the literature regarding the procedures for non-cryopreserved autologous PBSCs transplant in countries with limited resources. The bibliographical research of this work was limited onsites like PubMed, Googlescholar, using the following articles on the non-cryopreserved autologous PBPCs in hematological malignancies in developing countries have been selected. These papers were analyzed in terms of mobilization, apheresis, preservation and viability, conditioning regimen, engraftment, response and finally survival. This work sums up experience from 11 transplant centres which carried out autografts with non-cryopreserved PBPCs in 517 patients suffering from hematologic malignancies. The results in terms of mobilization showed a median CD34+ = 4.26 x10^6/kg in the MM and 4.47x10^6/kg in lymphomas, a viability > 90% and > 75% respectively in MM and lymphomas after a conservation of 24 to 144 hours at +4°C. The engraftment (ANC = 10.1 days, platelets = 14.07 days) and TRM (2.6%) were very satisfactory.

Conclusion: We conclude that this method is easy, efficient and safe. It is expected to grow in developing countries due to its low production cost and procedure simplicity.

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Introduction

Autologous bone marrow progenitor cells (BMPCs) or peripheral blood progenitor cells (PBPCs) is a supportive therapy that allows the use of high doses, intensive antitumoral chemotherapy in hematological malignancies[1,2]. Many studies have shown the superiority of autologous BMPCs or PBPCs over conventional chemotherapy in hematological malignancies such as multiple myeloma (MM)[3] or lymphoma[4-6]. PBPCs are currently used in autografts in hematological malignancies only and BMPCs are reserved to certain indications as haplo-identical allografts, or bone marrow failure. PBPCs are typically cryopreserved in liquid nitrogen at -180°C in dimethylsulfoxide (DMSO) and albumin[7-9]. Progenitor cells shouldbe washed and cleaned from DMSO prior to use in the patient. This preservation technique requires expensive equipment. In vitro study concerning the use of non-cryopreserved hematopoietic progenitor cells (HPCs)[10] was first published in 1957. It was then followed by studies on the conservation of PBPCs at +4°C[11-13] and their clinical use[14].

Very few autografts were performed with non-cryopreserved PBSCs and in our opinion there are no published, randomized or controlled, studies on the non-cryopreserved autologous PBPCs. Only two literature reviews on this topic study have been published. The first by Wannesson et al in 2007 on autologous HPC transplantation (bone marrow and peripheral blood) in hematological malignancies and solid tumors[15], and the second by Al-Anazi in 2012 on the autologous PBPCs transplantation in the MM[16]. The aim of our study is to report all published data in the field of non-cryopreserved autologous transplant in hematological malignancies in developing countries, to show their feasibility, safety and efficacy with the aim to promote this technology in countries with limited resources.

Methods

Bibliographic research was based on PubMed, and Google scholar, using the following keywords: hematopoietic, progenitor, non-cryopreservation and autograft. We then selected all the articles on the non-cryopreserved autologous PBPCs in hematological alignancies in developing countries. The selected papers were analyzed in terms of mobilization, apheresis, preservation and viability, conditioning regimen, engraftment, response and finally survival. Data from this review were synthesized in a descriptive manner. This included the tabulation of study characteristics and outcomes. In this review all the survival times were calculated from the date of transplant. Transplant-related mortality (TRM) was defined as any death related to a fatal complication in the absence of the underlying disease within 100 d from transplantation. Overall Survival (OS) was defined as the duration from the date of transplantation until death or date of follow-up when the patient was known to be alive. Progression-free survival (PFS) was calculated from the date of transplantation to disease progression or death (regardless of the cause of death). The OS and the PFS were determined using the Kaplan–Meier estimation with 95% confidence intervals from standards errors.

Results

Research on PubMed and other sites identified several publications and abstracts. Only 11 studies were selected, responding to the criteria concerning non-cryopreserved autologous progenitor cells transplant, in the developing countries. Countries of origin are by alphabetical order: Algeria, Colombia, Egypt, Greece, India, Iran, and Mexico. Morocco began using the PBPCs program in the autografts in two centers (Casablanca and Marrakech), but the results are not published yet. All the 11 studies published from 2000 to 2014, were a retrospective of "single center case series" type. The majorityfocused on the MM and lymphoma[17-26], and only one study focused on acute leukemia[18].

Mobilization

9 groups have performed PBPCs mobilization using G-CSF alone, while 2 groups have used G-CSF in combination with chemotherapy. In Multiple Myeloma, all studies[17,19,22,23,25,26] have conducted the mobilization with subcutaneous G-CSF alone at a dose of 15 µg/kg/day, or 5 µg/kg twice a day, for 4 to 5 consecutive days. In lymphomas, mobilization was performed using G-CSF (5µg/kg/day for 3 days) in combination with cyclophosphamide at a dose of 1.5 g/kg/day, for 3 days, in 2 groups[20,21].

Apheresis

The PBPCs apheresis was performed using devices as Haemonétics®, Cobe Spectra® or Optia®. Leukapheresis was started as soon as the flow cytometer counting of $CD34^+$ (Cluster differentiation) PBSCs was greater than 1 million cells/µl. The mean number of leukapheresis[17] was 2 in MM and 3 in lymphomas. In MM, the overall mean of $CD34^+$ collected was 4.26 x 10^6/kg (range, 0.32 to 27.8). It was of 4.47 x 10^6/kg (range, 1.9 to 24.6) in lymphomas.There was no report of mobilization failure in the published series.

Conservation

The PBPCs collected were saved in the refrigerator at +4°C for a period ranging from 1day to 6 days[11,13,9], depending on the type of conditioning regimen used. In the MM, storage time ranges from 1 to 2 days, and it was of 3 to 6 days in lymphoma (Table 1).

Table 1: Patients' characteristics and results of non-cryopreserved autologous peripheral blood progenitor cell transplantation.

Author	Patients Number	Age (years)	Diagnosis	High Dose Therapy	CD34+ reinfused	Storage condition
Papadimitriou et al. [17]	72	8-69	MM NHL HL	Mel 140-180/ MelVP16	3(0.8-27.8)	+4°C 24-60h
Ruiz-Argüelles et al. [18]	46	9-67	MM HL NHL AML ALL	Mel 200	4.68	+4°C 24-72h
Cuellar-Ambrosi et al. [19]	47	12-67	NHL MM	CBV/CTX-TBI/Mel 200	1.36 (0-6.32)	+4°C 144h
Mabed et al. [20]	28	16-50	HL	CTX/VP16/ Carboplatin	6.4 (3.8-24.6)	+4°C 72h
Mabed et al. [21]	32	17-55	NHL	CBDA/ VP16/CTX	>3	+4°C 72h
Lopez-Otero et al.[22]	26	42-66	MM	Mel200	7.56 (0.32-14.8)	+4°C 24h
Bekadja et al. [23]	54	35-65	MM	Mel 200	3.60 (1.90-10.52)	+4°C 24h
Ramzi et al. [24]	45		HL	CEAM	3.4	
Ramzi et al. [25]	38	NA	MM	Mel 140-200	NA	+4°C 48h
Kayal et al. [26]	92	22-65	MM	Mel 200	2.9 (0.9-7.67)	+4°C 48h
Bekadja et al.	45	17-46	HL	CBV/EAM/ BEAM	3.61 (2.90-21.05)	+4°C 72-144h

Viability

The viability of PBPCs was calculated by Trypan Blue technique and by flow cytometry[11,14,19]. The average viability was of over 90% in MM and over 75% in lymphomas.

Conditioning Regimen

The conditioning regimen and the myeloablative therapy were dependent on the diagnosis. In MM, all of the studies have used the melphalan at a dose of 180[17] or 200 mg/m² on D-1[17,19,22,23,25,26]. In lymphoma, the protocols used were of a different type: MEL 200 (Melphalan 200mg/m²), CBV (Cyclophosphamid, BCNU, Etoposide), BEAM (BCNU, Etoposide, Aracytin, Melphalan), CEAM (Lomustine, Etoposide, Aracytin, Melphalan), EAM (Etoposide, Aracytin, Melphalan), CEC (Cyclophosphamid, Etoposide, Carboplatin), MEL/VP16 (Melphalan, Etoposide) and their duration varies from 3 to 6 days (Table 2).

Table 2: High-dose therapy schedules employed in MM and lymphoma with non cryopreserved progenitor cells autologous transplant.

Disease	HDT combination	Dosage and schedule
Myeloma	Mel 180-200	Melphalan 200 mg/m^2[18] [19] [22] [23] [25] [26] Melphalan 180 mg/m^2[17]
Lymphoma		
	CBV	CTX 120mg/kg + etoposide 400mg/m^2 + BCNU 300 mg/m^2[19]
	MEL 200	Melphalan 200 mg/m^2 [18]
	MEL/ VP16	Melphalan 140 mg/m^2 + etoposide 1500 mg/m^2 [17]
	CEC	CTX 120 mg/kg + etoposide 30 mg/kg + carboplatine 400 mg/m^2 [20] [21]
	CEAM	Lomustine 200 mg/m^2+ etoposide 1000/ m^2 + cytarabine1000/m^2 + melphalan 140mg/m^2 [24]
	BEAM	BCNU 300mg/m^2 + etoposide + 800/ m^2 + cytarabine 800/m^2 + melphalan 140mg/m^2 (Bekadja)
	EAM	Etoposide 1000 mg/m^2 + cytarabine 1000 mg/m^{2}x2/d + melphalan 140mg/m^2 (Bekadja)

CTX: Cyclophosphamid; BCNU: Carmustin

Engraftment

Engraftment was defined by the rate of ANC (Absolute Neutrophil Count) over 500/µl and a platelet count greater than 20,000 /µl, except for one study in which the threshold was 25,000 platelets/µl[17]. The results of engraftment in the different studies are shown in Table 3. The overall mean recovery time of ANC was of 10.1 days (range, 6-27) and that of the platelets was of 14.07 days (range, 7-38). This recovery time was respectively 10 and 13 days in MM and 12 and 14,4 days in lymphoma. No engraftment failure was recorded among the different studies. The overall median rate of the transplant related mortality (TRM) was 2.6%, while it was 0% and 3% respectively in the MM and lymphoma.

Table 3: Results of engraftment with non-cryopreserved autologous peripheral blood progenitor cell transplantation.

Author	N patients	Neutrophils > 0.5 10^9/l (median days and range)	Platelets >20 10^9/l (median days and range)	TRM patient %	GF patient %
Papadimitriou et al. [17]	72	9 (6-16)	5 (0-89) > 25 109/l	0	0
Ruiz-Arguëlles et al. [18]	46	14 (0-86)	25 (0-102)	1 (2)	0
Cuellar-Ambrosi et al. [19]	47	11 (9-15); 13 (10-17)	16(11-44); 15(14-20)	6 (12.7)	0
Mabed et al. [20]	28	13 (7-18)	15 (7-20)	-	0
Mabed et al. [21]	32	12 (8-17)	14 (7-19)	3 (9.37)	0
Lopez-Otero et al. [22]	26	27 (0-53)	37 (0-73)	(9.6)	0
Bekadja et al. [23]	54	10 (6-17)	13 (9-24)	0	0
Ramzi et al. [24]	45	11	14	1 (2.2)	0
Ramzi et al. [25]	38	11 (9-21)	13 (10-31)	0	0
Kayal et al. [26]	92	10 (8-27)	14 (9-38)	3 (3.2)	0
Bekadja et al.	45	11 (8-22)	13 (10-24)	(3)	0

Post Transplant Results

Considering the heterogeneity of the studies in terms of diagnosis and intensification protocols, it is difficult to analyze them in relation to response or survival. However, the median follow-up period ranged between 10 and 38.8 months in the MM, and between 16 and 36 months, in lymphoma. The overall survival (OS) and disease free survival (DFS) in the MM and lymphoma are reported respectively in Table 4.

Table 4: Survival of patients with MM and Lymphoma autografts with non-cryopreserved PBPCs.

Author	Patients Number	Diagnosis	Follow-Up (median)	OS	PFS
Papadimitriou et al. [17]	33	MM	NA	NA	NA
Ruiz-Arguëlles et al. [8]	6	MM	NA	NA	NA
Cuellar-Ambrosi et al. [19]	10	MM	NA	NA	NA
Lopez-Otero et al. [22]	26	MM	NA	80% at 76 months	NA
Bekadja et al. [23]	54	MM	10 months	94% at 30 months	94% at 30 months
Ramzi et al. [25]	38	MM	31 months	30 months (median)	27 months (median)
Cuellar-Ambrosi et al. [19]	21	NHL	NA	NA	NA
Mabed et al. [20]	28	HL	16	45% at 24 months	42% at 24 months
Mabed et al. [21]	32	NHL	18	50% at 24 months	43% at 24 months
Ramzi et al. [24]	45	HL	27	27 months (mean)	20 months (median)
Bekadja et al.	45	HL	36	67% at 60 months	58% at 60 months

Discussion

PBPCs autologous transplant is indicated as first-line treatment in the MM[27-30], in the mantle cell lymphoma[31], as consolidation treatment in the diffuse large cell lymphoma[32,33] and as salvage therapy during relapsed or refractory forms of Hodgkin's diseases[34-38] or non-Hodgkin lymphomas[39,40]. The number of publications regarding non-cryopreserved autologous transplant is scarce because of the widespread use of the cryopreserved stem cells. In our work, we collected only 11 eligible studies: 10 published[17-26] and one non-published personal data, dealing with non-cryopreserved autologous transplant in hematological malignancies (lymphoma and MM) in some developing country, from 2000 to 2015. All these studies are of type of single-center, retrospective, non-randomized and uncontrolled, reflecting so the care of patients in real life as well as working conditions of countries with limited resources. Only one study is of prospective type, and included 26 patients with MM[22]. A total of 517 patients underwent a non-cryopreserved PBPCs autologous transplant including 259 MM, and 231 lymphomas with, in the latest, 135 Hodgkin's lymphoma.

Mobilization

The first step of the autograft is PBPC mobilization. There is no absolute rule in PBPC mobilization, but multiple studies have been published regarding recommendations for improving the harvesting efficiency of PBPCs[41-44]. Two main methods are used in PBPC mobilization, the first relates to the use of growth factor G-CSF (Growth Colony Stimulating Factor) alone, given subcutaneously at a dose of 10 to 15µg/kg/day or 5µg/kg twice a day, for 5 days[45,46], the second consists in the combination of G-CSF with chemotherapy[47]. There have not much difference in the performance of harvesting of $CD34^+$, but the second method requires hospitalization for the management of aplastic anemia secondary to chemotherapy, whereas in the first method, the use of G-CSF alone can be done at home, which reduces the costs of the autograft procedure. The majority of studies, have achieved mobilization with G-CSF alone especially in the MM and lymphoma, only two groups have used G-CSF in combination with cyclophosphamide[20,21]. The objective of the mobilization is to reach at least $2x10^6$/kg $CD34^+$ in the MM in which the conservation of $CD34^+$ is short (24 to 48 hours) and at least $4x\ 10^6$/kg in lymphomas in which the conservation of $CD34^+$ is more longest (3-6 days). Indeed, the optimal figure of $CD34^+$ necessary for hematopoietic reconstitution is not known with certainty and a minimum of 2.0 to 3.0 x 10^6 $CD34^+$ cells/kg is typically recommended. In this work, all the studies have achieved sufficient levels of $CD34^+$, that was 4.26 x 10^6/kg (MM) and 4.47 x 10^6/kg (lymphoma), to perform autografts, and no mobilization failure was reported.

Conservation and Viability

Many studies have shown the possibility tosave the PBPCs at +4°C in a refrigerator, for several days, with a final viability of over 80% that allows the achievement of autografts[11-14]. Preti et al showed that there was no difference in terms of viability and engraftment between conservation at +4°C and cryopreservation of PBPCs[13]. In addition, cryopreservation requires the use of a preservative liquid, dimethylsulfoxide (DMSO), which is responsible for several side effects[48-50] so that it requires a PBPCs washing before their use, on the in other hand, it allows a second transplantation if needed. In all published articles, the conservation at +4°C allowed the achievement of autografts with a satisfactory rate of viability of PBPCs despite retention periods up to three days, as in the study of Cuellar-Ambrosi et al[19], and of Bekadja et al (no published) where the conservation time was up to 6 days.

Therapeutic Intensification

By using high-dose chemotherapy (HD), therapeutic intensification is the most important part of the autograft procedure, as it has a direct anti-tumor effect. Since the 90s, the high-dose chemotherapy of Melphalan type at 200 mg/m^2 on D-1, followed by the autologous transplant of PBPCs, is considered the standard first-line treatment of MM for eligible patients to this procedure. So, the schedule consisting of administration of the HD chemotherapy (Melphalan) on D-1, enable the conservation of PBPCs at +4°C for only 24 to 48 hours, with an obtaining viability of $CD34^+$ cells over 95%, and is perfectly consistent with an autologous transplant of non-cryopreserved PBPCs. In lymphomas, the situation is very different; the intensification protocols used are shown in Table 2. These protocols such CBV[51], BEAM[52], or EAM include administration periods ranging from 3 to 6 days, which need a collection of $\geq 3x10^6$ $CD34^+$/kg for varying a viability of 75% to 85%.

The conservation of the PBPCs up to 7 or 8 days is then feasible, but needs to obtain a number of $CD34^+$ cells $\geq 3x10^6$ /kg at time of the reinfusion of the PBPCs. So, the major difficulty is in the mobilization, especially among patients who received multiple lines of therapy. In consolidation phase, especially in the mantle cell lymphoma or in the diffuse large B cell lymphoma(DLBCL)[53,54], the probability to obtain a number of $CD34^+$ cells $\geq 3x10^6$/ kg is very highview the low number of chemotherapy lines, and non-cryopreserved PBPCs can be used easily. The improvement of the autograft results in lymphomas will certainly with the reduction of the number of chemotherapy cycles, by early assessment of the PET scan response, and by availability of new intensification protocols, more myeloablative, as consolidation phase after the first-line induction. These regimens will allow the use of non-cryopreserved PBPCs, view the high possibilities of their mobilization.

Engraftment

Engraftment was evidenced by the rate of the ANC and platelets count. The aplastic phase was managed either with or without growth factor in case of profound neutropenia. Globally the median length of the ANC and platelets rate was similar to that of autografts using cryopreserved PBPCs[55] both in the MM[56] and lymphoma. Nevertheless in the lymphoma, duration was a little longer due to the number of previous chemotherapy and refractory nature of lymphoma[57-59]. Overall, these numbers show ahospitalizationless than 21 days in the MM and 25 days in the lymphoma, that which classifies the non-cryopreserved autologous transplant in the favorable group according to Lanza et al.[55]. No engraftment failure or complications related to the infusion of PBPCs were mentioned. In addition, among 517 autografts, 2.6% of patients died as a result of the procedure, particularly in the autologous transplant in lymphoma. This rate of TRM is comparable to that found in the literature; demonstrating the safety of non-cryopreserved autologous PBPC. Thus, the technique of autologous with non-cryopreserved PBPCs is a simple, reliable and feasible method. It is also safe, effective and less costly.

Very few teams in developing country use this procedure, whereas the need for care is important, especially in hematologic malignancies. The Eastern Mediterranean Bone Marrow Transplantation group, (EMBMT) who represents the Eastern Mediterranean Region (EMRO) comprising 10 countriesnamely, Algeria, Morocco, Tunisia, Egypt, Lebanon, Iran, Saudi Arabia, Pakistan, Jordan and the Sultanate of Oman. The 2008-2009 reporthas shownan activity rate of autografts of 36.5% (n = 483/1322 total first transplants) in these countries, versus59% (n = 16591/28033 total first transplants) in the developed-country[60]. The report also highlights the limited number of transplant centers in developing countries which is 14 versus 647, i.e. 46 time greaterfor 2009, in developed countries[61]. Moreover, the average number of Transplant Center is 14/country in the EBMT Group which count 48 countries in 2009 versus 1,4 /country in the EMBMT group which has 10 countries. The number of centers per 10 million inhabitants is respectively 7.6 and 0.3 in developed countries versus developing countries, and the number of transplants per 10 million inhabitants is 467 and 28.7 in

the EBMT and EMBMT Groups respectively. So this situation showed that new transplant centers and particularly the development of the non-cryopreserved autologous PBPCs transplant in these countries and other resource-constrained countries are necessary.

Conclusion

In conclusion, autologous PBPCs transplant is very suitable for therapeutic limited-resource countries. Its interest is its simplicity of implementation, its lower cost and ability to autograph a large number of patients.

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