ORIGINAL ARTICLE

Characteristics of autologous peripheral blood stem cells collection over a one-year period

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ABSTRACT

Aim To present characteristics of collecting autologous peripheral blood stem cells over a one-year period with an emphasis on efficiency and safety.

Methods A retrograde analysis of 24 leukapheresis in 20 adult patients with malignant haematological diseases in the Blood Transfusion Institute of the Federation of Bosnia and Herzegovina in Sarajevo, was done. Cell separators Amicus and Spectra Optia were used for collection procedures.

Results The patient's age ranged from 27 to 65 years. Target cells were collected in one procedure in sixteen patients, while in four patients they were collected in two procedures. The mean CD34+ collection efficiency was 57.7%. The median number of CD34+ cells and percentage of CD34+ cells in the products were 5.52x10e6/kg (range 3.28-9.00) and 1.57% (range 0.96-2.91). A strong positive correlation was found between the number of CD34+ cells in peripheral blood on the apheresis day and the amount of CD34+ cells collected in the products (r_s=0.73). A total of 95% of patients collected the amount of ≥3x10e6/kg and 55% of ≥5x10e6/kg CD34+ cells for a single transplant. A decrease in platelet count, haemoglobin and haematocrit values after the procedure was not significant. Potassium decrease showed statistical significance (p<0.000). Adverse events occurred during one procedure (4.2%)**.**

Conclusion A low number of adverse events and good collection efficiency with adequate patient monitoring, indicate that leukapheresis is a safe procedure that is successfully used in the autologous transplantation process in the treatment of malignant haematological diseases.

Key words: CD34, hematopoietic stem cells**,** leukapheresis

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Original submission:
20 March 2020;
Revised submission:
04 May 2020;
Accepted:
28 May 2020
doi: 10.17392/1171-20

Med Glas (Zenica) 2020; 17(2): 290-296

INTRODUCTION

In the last twenty years, peripheral blood stem cells (PBSCs) collection by apheresis, as an efficient and safe method, has replaced the bone marrow as a source for autologous transplantation in the treatment of patients with malignant haematological diseases (1-4). The PBSCs transplantation has been used as a treatment in different haematological and non-haematological diseases (3). Peripheral blood cells in the cell separator used for collection are stratified by differential centrifugation with respect to specific density, with consequent separation and collection of needed mononuclear cells (MNC) and the return of other blood cells to the patient (2).

The PBSCs are present in a population of blood cells that express the CD34 marker on the surface membrane, located within a mononuclear cells layer (1).

During the collection, a small number of other cells are also collected at the same time. Apheresis procedure can be accompanied by certain symptoms related to withdrawal of blood into cell separator, vascular access or metabolic changes (2).

Normally, a small number of PBSCs are found in peripheral blood and their mobilization stimulates their exit from the bone marrow into the peripheral blood (3). Common mobilization strategies include the use of granulocyte stimulating growth factor alone or in combination with chemotherapy (3,4). An increase in the number of cells is greater with their combination (4).

After the collection, autologous PBSCs undergo cryopreservation and adequate storage up to the time of reinfusion in the transplant process (5).

Transplantation of autologous PBSCs is a method of treatment which provides reconstitution of hematopoietic system of the patients whose disease is primary eradicated by myeloablative therapy with or without irradiation, and irreversible bone marrow damage is overcome by infusion of previously collected and PBSCs preserved by freezing (1,4). Sufficient amount of hematopoietic stem cells is an important predictor for successful transplantation (3).

Studies on this topic in our country are insufficient. There is a study assessing influence of peripheral CD34+ cells number on collected CD34+ cells number in one day collection (6). In our study, the focus was on the collection procedure, as well as on the patient during that procedure and on the parameters resulting from it, so it seems important sharing experience with performing this kind of the procedure in the autologous transplantation process to the local and general professional community.

The aim of this study is to present the characteristics of collecting autologous PBSCs over a one-year period, with an emphasis on efficiency and safety.

PATIENTS AND METHODS

Patients and study design

A retrospective analysis of 24 leukapheresis procedures for the collection of autologous PBSCs in 20 adult patients at the Blood Transfusion Institute of the Federation of Bosnia and Herzegovina in Sarajevo was done. Data over a one-year period, from December 2017 to December 2018 were analysed. Those were the patients from the Clinic for Haematology, University Clinical Centre in Sarajevo with malignant haematological diseases who are involved in the process of autologous transplantation. During that process they undergo apheresis procedures for the collection of PBSCs and their cryopreservation and storage at the Department for Haemapheresis with Blood Bank at the Blood Transfusion Institute of the Federation of Bosnia and Herzegovina in Sarajevo.

There were eight (40%) male and 12 (60%) female patients, whose age ranged from 27 to 65 years (mean 48), body weight ranged from 45 to 115 kg (mean 74) and body height ranged from 155 to 187 cm (mean 170).

Patients with completed medical documentation were taken for analysis. All patients signed a statement and a consent for the entire process of autologous peripheral hematopoietic stem cell transplantation with the consent of a member of the Ethics Committee of University Clinical Centre in Sarajevo that the ethical principles were met. All the analyses covered by this study are standard analysis performed during the whole procedure of the collection of hematopoietic stem cells from peripheral blood in the process of autologous transplantation. The research was approved by the Expert Council of the Blood Transfusion Institute of the Federation of Bosnia and Herzegovina.

Methods

The mobilization process included the use of chemotherapy followed by daily stimulation with granulocyte-stimulating growth factor (G-CSF) - biosimilar filgrastim (Zarzio, Sandoz, GmbH). Mobilization strategies for PBSC for myeloma patients were performed with cyclophosphamide 2-4 gr/m^2 for two days with the addition of G-CSF 5-10 mg/m^2 starting from the third day until leukapheresis, during the first complete remission or very good partial remission, mostly after 4-5 prior chemotherapy cycles. In some myeloma patients cyclophosphamide dose was adjusted due to renal impairment. Myeloma patients were planned for two transplantations.

In Hodgkin's lymphoma patients, mobilization strategies included dexamethasone, cytarabine, cisplatin (DHAP) with G-CSF 5-10 mg/m^2 starting from the fifth day until leukapheresis, during the first relapse and in one patient with refractory disease.

Mobilization strategies for non-Hodgkin's lymphoma patients included DHAP, cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP), cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone (CHOEP) and etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin (DA-EPOCH) with G-CSF 5-10 mg/m^2, also starting from the fifth day until leukapheresis. Five mantle cell lymphoma patients were mobilized with one of the therapeutic cycles, when bone marrow was without lymphoma cells infiltration. Three diffuse large B cell lymphoma patients with high International Prognostic Index (IPI) score were mobilized during the first line therapy and one anaplastic lymphoma kinase (ALK)-positive patient was mobilized during therapeutic cycles when bone marrow was without lymphoma cells infiltration. Prior chemotherapy cycles in non-Hodgkin's lymphoma patients included CHOEP, R-CHOP (rituximab + CHOP)/DHAP, R-CHOEP (rituximab + CHOEP)/DHAP, DA-EPOCH, R-DA-EPOCH (rituximab + DA-EPOCH), while in Hodgkin's lymphoma patients DHAP and bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP).

Complete blood cell count was evaluated daily after mobilization with chemotherapy. The number and percent of CD34+ cells in the peripheral blood and in the leukapheresis product, also their viability were counted by flow cytometry. CD34+ cells counting started when peripheral blood leukocyte counts were >1x10e9/L. The leukapheresis process was initiated when the CD34+ cell count in peripheral blood on the apheresis day was >15x10e6/L and platelet count >30x10e9/L.

All patients had an inserted central venous catheter to sustain an adequate inlet flow rate during apheresis. If some problem occurred with central venous catheter, peripheral apheresis/dialysis needles (17 GA, Fresenius Medical Care, Bad Homburg, Germany) were used in peripheral veins.

Leukapheresis for PBSC collection was performed with a continuous flow blood cell separators - Amicus (Fresenius Kabi, Bad Homburg, Germany; version 4.4) and Spectra Optia (Terumo BCT, Lakewood, CO, USA; version 7, 11) with MNCs collection protocol. Extracorporeal blood volumes were 160 mL and 191 mL. Patients were connected to the cell separator by their centrally or peripherally inserted venous catheter. One line was used to withdraw blood out of the patient and into the separator, and the other line was used to return processed blood back to the patient. Collections can occur on a daily basis until target CD34+ cells levels are achieved. For extracorporeal anticoagulation anticoagulant citrate dextrose solution formula A (ACD-A) was used at the ratio of 12:1 (whole blood: anticoagulant). Daily PBSCs collections were performed in order to reach a yield of ≥3x10e6/kg or an optimal yield of ≥5x10e6/kg CD34+ cells in the leukapheresis product required for a single transplant. Peripheral blood electrolyte values (Na, K, Ca, Cl) were determined before and after leukapheresis. All patients received prophylactic intravenous calcium infusion before leukapheresis. Patient's blood pressure and heart rate were monitored during procedures and all adverse events were recorded.

Right after the collection, cell products were frozen using the controlled rate freezer (Consarctic BIOFREEZE BV45 Freezer, Schollkrippen, GmbH). Cryopreserving solution contained 10% dimethyl sulfoxide (DMSO) in autologous plasma. A number of bags used for cryopreservation (CryoMACS Freezing Bag 500, 750, Miltenyi Biotec, GmbH) depended on the product volume and cell numbers. Cryopreserved products were stored in a container with liquid nitrogen at temperature from -150-196 °C (Consarctic BSF 350, Schollkrippen, GmbH) until reinfusion.

Statistical analysis

The distribution of data from the study was tested for normality by Kolmogorov-Smirnov test. The results are presented as arithmetic means ± standard deviation (SD) or medians with a range, depending on the data distribution. The significance of the difference in peripheral blood cell counts and electrolyte values before and after the procedure were analysed by non-parametric Wilcoxon matched pairs test. The association between peripheral and collected CD34+ cells was assessed with non-parametric Spearman correlation. For all comparisons, the level of statistical significance was $p<0.05$.

RESULTS

The total blood volume of analysed patients varied from 3097 to 6446 mL (mean 4586 mL). Out of the total of 20 patients, five (25%) were patients with Hodgkin's lymphoma, nine (45%) with non-Hodgkin's lymphoma and six (30%) with myeloma multiplex. Most of the patients, nine (45%), were A+ blood type (Table 1).

Table 1. Characteristics of 20 haematological patients who underwent 24 leukapheresis procedures for the collection of autologous peripheral blood stem cells

Characteristics	Value
Diagnosis No (%)	
Hodgkin's lymphoma	5 (25)
Non-Hodgkin's lymphoma	9 (45)
Myeloma multiplex	6 (30)
Gender No (%)	
Male	8 (40)
Female	12 (60)
ABO blood type No (%)	
O+	3 (15)
A+	9 (45)
B+	3 (15)
O-	3 (15)
A-	2 (10)
Age (±SD/range) (min-max) (years)	48.40±12.61 (27-65)
Weight (±SD/range) (min-max) (kg)	74.30±18.60 (45-115)
Height (±SD/range) (min-max) (cm)	170.5±9.105 (155-187)
Total blood volume (±SD/range) (min-max) (mL)	4586±1011 (3097-6446)

SD, standard deviation

Processed total body blood volume during leukapheresis procedures varied from 4908-21593 mL (mean 12755). The leukapheresis procedures lasted from 193-395 min. (mean 293.5), which was an average of 5 hours. The CD34+ collection efficiency ranged from 26-95% (mean 57.7), and the percentage of platelet reduction ranged from 3.9-36% (mean 20) (Table 2). The median number of CD34+ cells count and mononuclear cells count in the product in all procedures were 5.52x10e6/kg (range 3.28-9.00) and 1.51x10e8/kg (range 1.09-2.28). The median haemoglobin and haematocrit values in the collected product were 6.45 g/L (range, 4.68-18.00), and 2.17% (range 0.79-5.48), respectively, while the median platelet count in the product was 478.5x10e9/L (range 332-677). The median viability of CD34+ cells in the product after leukapheresis was 98.75% (range 98-99.05) (Table 2).

Table 2. Leukapheresis procedure and product parameters

Procedure parameters	x ± SD	Range (min-max)
Processed total body volume (mL)	12755±3959	4908-21539
AC volume (mL)	1160±345.1	453-1949
Inlet blood flow rate (mL/min)	50.17±10.33	32.60-75
Procedure time (min)	293.5±48.43	193-395
Product volume (mL)	143.6±57.54	64-262
Platelet reduction (%)	20±12.10	3.9-36
CD34+ collection efficiency CE (%)	57.7±17.48	26-95
Product parameters	**Median**	**Range**
CD34+ cells x10e6/L	2728	2028-4612
CD34+ cells (%)	1.57	0.96-2.91
Haemoglobin (g/L)	6.45	4.68-18.00
Haematocrit (%)	2.17	0.79-5.48
Platelets x10e9/L	478.5	332-677
Mononuclear cells x10e9/L	83.20	60.20-107.2
Leukocytes x10e9/L	173	156.3-202.8
CD34+ cells x10e6/kg	5.52	3.28-9.00
Mononuclear cells x10e8/kg	1.51	1.09-2.28
Viability of CD34+ cells (%)	98.75	98-99.05

AC, anticoagulant; CE, collection efficiency; x, mean; SD, standard deviation

Table 3. Characteristics of patients, number of collected cells per patient and number of bags used for cryopreservation per patient

Ordinal patient No	Diagnosis	No. of procedures	CD34+ (x10e6/kg)	CD34+ (%)	No. of bags used
1.	NHL	1	5.40	1.85	3
2.	NHL	1	10.6	3.42	2
3.	NHL	1	7.66	1.32	4
4.	NHL	2	4.86	0.88	8
5.	NHL	1	5.17	2.70	2
6.	NHL	1	3.18	1.44	2
7.	MM	1	6.30	1.30	2
8.	NHL	1	5.64	1.70	2
9.	NHL	1	3.77	0.91	3
10.	NHL	1	19.67	6.53	3
11.	HL	1	14.96	4.51	2
12.	HL	1	6.07	1.43	4
13.	HL	1	13.20	4.90	3
14.	HL	1	8.68	3.80	2
15.	HL	1	3.60	1.11	4
16.	MM	2	6.40	2.07	4
17.	MM	1	5.80	1.86	3
18.	MM	2	12.32	5.63	4
19.	MM	1	9.11	2.08	2
20.	MM	2	7.24	1.24	4

NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma; MM, Myeloma multiplex

In 16 (80%) patients, the collection of the target yield was performed with one procedure, while in four (20%) patients it was performed with two procedures on two consecutive days. The median CD34+ cells count and percentage of CD34+ cells in the leukapheresis product in all patients were 6.35x10e6/kg (range 5.34-9.48) and 1.86% (range 1.32-3.52), respectively. The mean number of bags used for cryopreservation after the completion of the collection in all patients was 3.15 (range 2-8) (Table 3).

A decrease in platelet count, haemoglobin and haematocrit values in peripheral blood after leukapheresis was observed, without statistical significance (p=0.139 and p=0.714, respectively). The median number of circulating CD34+ cells in peripheral blood on apheresis day was 62x10e6/L (range 28.99-89.38). Calcium and potassium values in peripheral blood decreased after the procedure, where the decrease in potassium showed statistical significance (p<0.000) (Table 4).

Table 4. Peripheral blood and electrolytes parameters before and after leukapheresis

Parameter	Median/range (before)	Median/range (after)	p
Leukocytes x 10e9/L	9.06 (4.33-16.55)	17.55 (8.87-29.28)	<0.001
Erythrocytes x 10e9/L	3.45 (3.02-3.74)	3.45 (3.09-3.77)	0.748
Platelets x 10e9/L	77.20 (66.08-93.35)	69.05 (59.60-98.48)	0.422
Haemoglobin (g/L)	103 (90.88-109.3)	98.45 (92.05-105.8)	0.139
Haematocrit (%)	31.10 (28.20-32.48)	31.05 (28.13-32.78)	0.714
Mononuclear cells x 10e9/L	2.15 (1.23-2.71)	2.29 (1.62-3.26)	0.007
CD34+ cells x10e6/L	62 (28.99-89.38)	-	-
Calcium (mmol/L)	2.25 (2.13-2.32)	2.22 (2.13-2.39)	0.324
Potassium (mmmol/L)	4.30 (3.80-4.80)	3.50 (3.02-3.80)	<0.000

A strong positive correlation was found between the number of circulating CD34+ cells in peripheral blood on the apheresis day and the amount of CD34+ cells collected in the products (r_s=0.73) (Figure 1).

Adverse events occurred during one procedure (4.2%) due to impaired blood flow through one of the lines of central venous catheter.

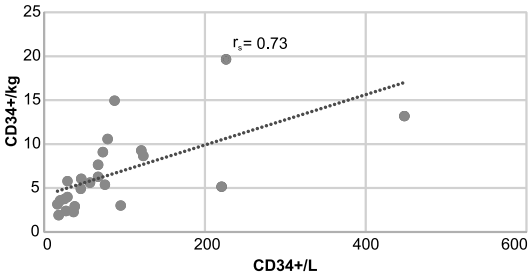

Figure 1. Correlation of collected CD34+ cells counts with peripheral blood CD34+ cell count in all procedures
r_s: Spearman's correlation coefficient

DISCUSSION

The PBSCs are usually collected during the hematologic recovery phase after mobilizing agents have been administered and the time of onset of the collection depends on the type of the disease and patients characteristics (2-4). The mobilization process may be accompanied by adverse events (2). Administration of chemotherapy causes bone marrow aplasia, so patients are usually cytopenic prior to collection, which applies specifically to peripheral blood platelet counts (2). In our study, 20% received a platelet transfusion prior to leukapheresis with the aim of raising the platelet count to >30x10e9/L.

In autologous collection, in case of inadequate peripheral veins, central venous catheters may be used for the collection due to the need for sufficient blood flow through the cell separator (7). During one procedure, one of our patients experienced problems with venous flow through inlet line of the central venous catheter and the procedure was continued using a peripheral vein for the inlet line of blood flow.

In leukapheresis procedures, for extracorporeal anticoagulation citrate-based anticoagulation is preferred over heparin anticoagulant solution for the reasons of lower cost, safety, effectiveness and rapid systemic clearance (8). The most commonly used anticoagulant solution is ACD-A (5,8). Cell separators use total blood volume to calculate the anticoagulant infusion rate delivered to the patient (8). Citrate anticoagulation causes metabolic changes such as hypocalcemia, hypokalemia, hypomagnesaemia, other electrolyte derangements and metabolic alkalosis that may be accompanied by appropriate symptoms (8). The most common reactions during apheresis procedures are principally related to the effect of hypocalcemia (2,8).

Factors influencing symptoms development include the rate of citrate infusion, the rate of decline in ionized calcium levels and hepatic metabolism of the infused citrate (8). All patients in our study received an intravenous calcium gluconate solution to prevent the onset of symptoms of hypocalcemia, which could occur during the procedure due to the use of citrate anticoagulant solution. During the procedure patients also drank an oral solution of effervescent calcium tablets. There is considerable individual variability in the development of symptoms and signs of citrate-induced hypocalcemia (8). Prophylactic oral calcium supplementation or an infusion of intravenous calcium can be effective in reducing severity and the incidence of citrate-induced symptoms during the procedures (1,8). In our study, the median calcium value after the leukapheresis procedure was lower than the values before, although this decrease was not statistically significant, while the median potassium value after the procedure was significantly lower. One patient received oral solutions of effervescent potassium tablet at the beginning of both procedures during two consecutive days, because of low levels of potassium before them. Oral potassium supplementation is a sufficient measure for the correction of hypokalemia and it should be administered only in patients with lower levels before leukapheresis (1). None of our patients experienced problems that could be associated with a decrease of electrolyte levels. Leukapheresis procedures may be accompanied by other side effects such as hypotension, hypertension, nausea/vomiting, headache, vertigo (9). However, any of these side effects did not occur in our patients.

Extracorporeal blood volume during leukapheresis depends on the type of the used cell separator, but when it comes to adult patients, mostly it does not present a problem because of a small volume of blood outside circulation (2).

During the PBSC collection, with mononuclear cells a portion of other cells is always collected, especially from the platelet layer, so the platelet count always decreases (10,11).

In our study, there was a decrease in the platelet count, haemoglobin and haematocrit values after the procedure, although this decrease was not statistically significant. The mean platelet percentage decrease in this study was 20% and no patient required transfusions after the procedure. Other authors report an average reduction in the platelet count after leukapheresis by 43% and 40-45% depending on the type of the used cell separator and the length of the procedure (2,10).

The mean collection efficiency of CD34+ cells by cell separators in this study was 57.7%. Other authors in their studies report an average collection efficiency of 42-43% and 50-55% depending on the type of the used cell separator (10,11).

A strong positive correlation in our study was found between peripheral blood $CD34^+$ cell count and the final $CD34^+$ cell collection, and on the basis of this and other studies this strong correlation shows that the number of peripheral CD34+ cells was the best predictor of the amount of CD34+ cells collected in the product per leukapheresis (1,12). There is still no consensus on the amount of blood stem cells needed to be infused to achieve adequate hematopoietic recovery. Reportedly, the safe minimum dose of CD34+ cells in the leukapheresis product for single transplant is still an amount of $\geq$2x10e6/kg (6, 12-19). Lower counts will be the concomitant risk of delayed neutrophil and platelet engraftment (19). Recommended stem cell collection target is 3-5x10e6/kg CD34+ cells in the product (5,12,16). Reinfusion of 5x10e6/kg CD34+ cells results in prompt engraftment and should be a preferred target or an optimal target for successful transplantation (19,20). Higher doses of target cells can result in faster engraftment, with the balance between targets and the number of apheresis procedures required to attain them (16). The collection of PBSCs for autologous transplantation is a well-established process (21). The number and viability of CD34+ cells is a surrogate for predicting successful engraftment (21).

In conclusion, the leukapheresis procedure is fully automated and involves the use of standardized cell collection protocols. The results of this study, such as low number of adverse events and good collection efficiency with adequate patient monitoring, indicate that leukapheresis is a safe procedure that is successfully used in the autologous transplantation process in the treatment of malignant haematological diseases.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interest: none to declare.

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