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Collection and Composition of Autologous Peripheral Blood Stem Cells Graft in Patients with Acute Myeloid Leukemia: Influence on Hematopoietic Recovery and Outcome

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A B S T R A C T

Hematopoietic stem cell (HSC) transplantation is a standard approach in the treatment of hematological malignant diseases. For the last 15 years the main source of cells for trasplantation have been peripheral blood stem cells (PBSC). With the availability of hematopoietic growth factors and understanding the advantages of treatment with PBSC, the application of bone marrow (BM) was supplanted. The aim of this survey was to explore the success of PBSC collection, the factors which influence the success of PBSC collection, the composition and the quality of graft and their infuence on hematopoietic recovery and outcome after transplantation in patients with acute myeloid leukemia (AML). PBSC were collected by the method of leukapheresis after applying a combination of chemotherapy and growth factors or only growth factors. The quality of graft was determined with the clonogenic progenitor cell assay and with the flow citometry analysis. Of the total 134 patients with AML, who were submitted to HSC mobilization, the collection was successful in 78 (58.2%) patients. The collection was more successful after the first than after the second attempt of HSC mobilization (49% vs. *11%). The criteria for effective mobilization were the number of leukocytes* $>3\times10^9$*/L and the concentration of CD34$^+$ cells* $>20\times10^3$*/mL in the peripheral blood on the first day of leukapheresis. The number of CD34$^+$ cells infused had the strongest impact on hematopoietic recovery. We noted significantly faster hematological recovery of neutrophils and platelets, fewer number of transfused units of red blood cells and platelets, shorter duration of the tranfusion support, shorter treatment with intravenous antibiotic therapy and shorter hospitalization after PBSC compared to BM transplantation. These advantages could provide their standard application in the treatment of patients with AML.*

Key words*: acute myeloid leukemia, autologous peripheral blood stem cells, graft composition, stem cell transplantation*

Introduction

Contemporary treatment of patients with acute myeloid leukemia (AML) begins with the induction chemotherapy in order to achieve a complete remission (CR)[1]. Leukemic cells are further removed with the intense consolidation chemotherapy. Yet there is no standard for further treatement[2]. It is possible to apply chemoterapy[3], allogenic stem cell transplantation transplantation (Allo--SCT) or autologous stem cell transplantation (ASCT). ASCT is adapted to wide population of patients who have certain restrictions for treatment with Allo-SCT, such as >45 years of age or unavailability of HLA matched donor hematopoietic stem cells (HSC). ASCT, unlike Allo-SCT has a higher incidence of relapse that is explained with the absence of positive immunological graft *versus* leukemia reaction (GLR), insufficient *in vivo* purging with consolidation chemoterapy and with the infusion of re-

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sidual leukemic cells together with the HSC graft. Lower incidence of transplant-related mortality (TRM) is explained with the absence of graft-*versus*-host disease reaction (GVHD).

ASCT can be performed using HSC from bone marrow (BM) or peripheral blood (PB). Given the numerous advantages such as, faster hematopoietic recovery, lower rates of morbidity and mortality, shorter hospitalization, lower costs of treatment and the possibility of applying high-dose chemotherapy to an older group of patients[4–6], peripheral blood stem cells (PBSC) has pushed the application of HSC from BM[7]. Before collecting, PBSC have to be mobilized from BM. For this purpose, the most effective is combined application of consolidation chemotherapy and growth factors[8–10] and it should be implemented after *in vivo* depletion of leukemic cells, and before hematopoietic exhaustion of BM[11,12]. Concentration of circulating $CD34^+$ cells in PB is taken as a good indicator for making decision about when to start leukapheresis[13–15]. The minimum yield of $CD34^+$ cells which allows quick hematopoietic recovery is 2×10^6 cells/kg. The optimal yield of $CD34^+$ cells that tends to achieve faster recovery is 5×10^6 $CD34^+$/kg. However, the duration and the number of leukapheresis procedures is individual and depends on mobilization therapy, previous chemotherapy and stage of disease. Processing a large volume of blood, by large volume leukapheresis (LVL), larger number of $CD34^+$ cells are collected and therefore LVL is the best choice in patients previously treated with numerous cycles of chemoterapy[16–18]. Infusion of larger number of $CD34^+$ cells and colony-forming-units-granulocyte-macrophage (CFU-GM) results in faster recovery of platelets and neutrophils[10,16–19]. The quality of collecting, processing and cryopreservating HSC product is provided by the American Association of Blood Banks (AABB) and the Foundation for the Accreditation of Hematopoietic Cell Therapy (FACT) standards[20,21]. It includes determination of $CD34^+$ cells quantity by flow cytometry and determination of HSC viability and clonogenicity by clonogenic progenitor cell assay[26]. The main criterion of the HSC product quality is its repopulation ability after transplantation.

In patients with AML, many parameters related to mobilization, collection and quality of the graft are not defined with certainty. Impact of the graft composition on the kinetics of hematopoietic recovery as well as on the outcome is unknown. In this retrospective analysis we investigated the influence of various factors on the success of leukapheresis procedure in patients with AML and explored the relationship between the composition of the graft and the hematopoietic recovery, lowering the need for transfusion support and the frequency of complications.

Patients and Methods

Patients aged ≤45 years, who had HLA matched donor of HSC, were treated with Allo-SCT. All other patients, aged ≤60 years, were candidates for treatment with ASCT and they received mobilization therapy in order to collect stem cells. During the 1995–2005 period, 134 patients with AML were submitted to stem cell mobilization. Diagnosis of AML was made by cytologic analysis of PB and BM, completed with cell immunofenotyping, cytogenetic and molecular analysis.

Treatment program

Induction therapy consisted of daunorubicine, idarubicine or mitoxantrone in combination with Ara-C and etopozide (DCE, ICE or MICE). CR was achieved if in BM <5% blast cells were found. Afterwards, the consolidation intensive chemotherapy was applied, which consisted of daunorubicine, mitoxantrone or idarubicine and intermediate-doses of Ara-C (DIA, IDIA or NOVIA). On the day 16, for the purpose of HSC mobilization, granulocyte growth factor (G-CSF, Neupogen, Roche, Switzerland) in a dosage of 10 μg/kg/bw. s.c. daily was started until the end of collection.

Collecting, processing, cryopreservation and storage of hematopoietic progenitor cell product

HSC were collected from PB using cell separator (COBE Spectra: Version 6.0. Gambro BCT, Lakewood, USA). Collecting was started when the number of $CD34^+$ cells in the peripheral blood was $>10\times10^6$/L. Duration of procedure was 4 hours[23]. The minimum yield was 2×10^6/kg bw.[24,25], and the optimum was between 3.5 and 5×10^6 $CD34^+$ cells/kg bw.[26]. In patients who failed to collect a sufficient number of HSC, the procedure was repeated or BM was taken from the posterior iliac crest, under sterile conditions, under general anesthesia, three days after application of G-CSF (10 μg/kg/bw. sc). The amount of BM was about 10–15 mL/kg/bw. To final apheresis product, autologous plasma and 10% dimethyl-sulfoxide were added. The product was frozen under controlled conditions in Planner Biomed Kryo 10^5 and stored in a liquid nitrogen container at –196 °C. Clonogenic progenitor cell assay, using MethoCult medium H4433 (StemCell Technologies, Vancouver, BC, Canada), was used to determine the number of cells that generate CFU-GM[27]. The number of $CD34^+$ cells was determined with flow cytometry (FACScan and FACSCalibur, BD Biosciences) by using the International Society for Hematotherapy and Graft Engineering (ISHAGE) protocol[22]. Monoclonal antibodies used were anti-CD45-FITC and anti-CD34-PE (BD Biosciences, Heidelberg, Germany).

Patient monitoring

During induction and consolidation therapy and after transplantation, clinical condition of patients was observed, including signs of infections and bleeding and the presence of other complications. Hematopoietic recovery implied number of neutrofils $>0.5\times10^9$/L and platelets $>20\times10^9$/L, without tranfusion support.

Autologous stem cell transplantation

Before transplantation patients had received myeloablative chemotherapy, which consisted of high dose bu-

sulfan 16 mg/kg/bw. orally and cyclophosphamide 120 mg/kg/bw. iv. or in minority of patients of fractionated total-body irradiation 1200 cGy total dose and cyclophosphamide 120 mg/kg/day iv. Immediately before infusion, HSC product was thawed in a sterile normal saline bath and infused to patient through a central venous catheter.

Statistical methods

This is retrospective research. The results were processed by statistical software SPSS 17.0. Statistical significance of differences between two arithmetic means was tested using the t-test and between more arithmetic means using the f-test. When analyzing correlations between variables Pearson (r_p) and Spearman correlation coefficient (r_s) were used. Hematopoietic recovery after ASCT was analyzed with the Kaplan-Meier statistical method and the log-rank test. The value of 0.05 was taken as the level of significance.

Results

Of the total 134 patients, 112 (83.6%) had *de novo* AML, 15 (11.2%) had secondary AML and 7 (5.2%) patients had unclassified AML (Table 1). After induction chemotherapy, which usually consisted of daunorubicune (74.6%), idarubicine (12.7%) or mitoxantrone (6.0%) in combination with Ara-C and etopozide (DCE, ICE or MICE), CR was achieved in 91 (67.9%) patients. All patients were not treated with ASCT; 5 patients did not yield enough CD34+ cells for transplantation, 5 patients had relapse of disease, 2 patients had acute hepatitis B, while in 2 patients CFU-GM colonies did not grow in culture

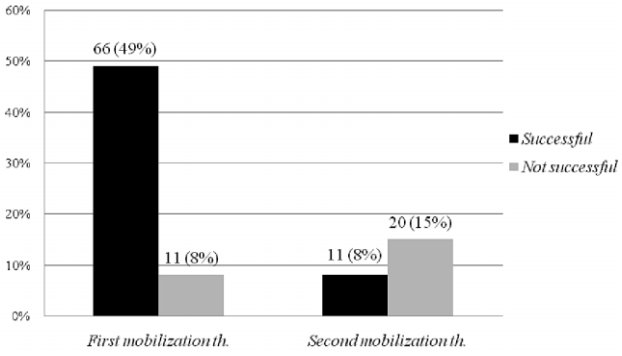

*Fig. 1. Success of CD34+ cell collection from peripheral blood *Of total number of patients (N=134), in 26 patients leukapheresis was not done.*

TABLE 1
PATIENTS CHARACTERISTICS (N=134)

Sex (m/f)	55/79
Age (median, range)	45 (4–61)
FAB subtype (%)	
M0	4 (3.0)
M1	15 (11.2)
M2	56 (41.8)
M3	2 (1.5)
M4	14 (10.4)
M5	16 (11.9)
M6	4 (3.0)
M7	1 (0.7)
AML sec.	15 (11.2)
AML unclasified	7 (5.2)
No. of chemotherapy cycles to CR (%)	
1 cycle	91 (67.9)
2 cycles	29 (21.6)
Unknown	14 (10.4)
Disease stage (%)	
CR1	107 (79.9)
CR2	7 (5.2)
Relapse	5 (3.7)
NA	15 (11.2)
Diagnosis – ASCT interval, months (median, range)	6 (3–14)

CR – complete remission, CR1 – first complete remission, CR2 – second complete remission, NA – non available, ASCT – autologous stem cell transplantation

TABLE 2
DETAILS OF PATIENTS TREATMENT (N=134)

Induction chemotherapy (%)	
DCE	100 (74.6)
ICE	17 (12.7)
MICE	8 (6.0)
Other	9 (6.4)
Mobilization chemotherapy (%)	
DIA	72 (53.7)
IDIA	17 (12.7)
NOVIA	8 (6.0)
ICE	8 (6.0)
Other	29 (21.6)
Transplantation (%)	
Transplantated	115 (85.8)
Not transplantated	14 (10.5)*
NA	5 (3.7)
Transplantat type (N=115) (%)	
BM	22 (19.1)
PBSC	71 (61.8)
BM + PBSC	22 (19.1)

DCE – daunorubicine + Ara-C + etopozide, ICE – idarubicine + Ara-C + etopozide, MICE – mitoxantrone + Ara-C + etopozide, DIA – daunorubicine + intermediate-doses of Ara-C, IDIA – idarubicine + intermediate-doses of Ara-C, NOVIA – mitoxantrone + intermediate-doses of Ara-C, NA – non available, BM – bone marrow, PBSC – peripheral blood stem cells

* 14 patients were not treated with ASCT; 5 patients did not yield enough CD34+ cells for transplantation, 5 patients had relapse of disease, 2 patients had acute hepatitis B, while in 2 patients CFU-GM colonies did not grow in culture

TABLE 3
GRAFT CHARACTERISTICS AFTER THE FIRST AND THE SECOND MOBILIZATION OF HEMATOPOIETIC STEM CELLS (N=108)*

	First mobilization therapy	Second mobilization therapy
Number of leukaphereses	2 (1–5)	2 (1–5)
Total harvest (median, range)		
Total nucleated cells, $x10^8$/kg	9.77 (1.30–34.45)	11.11 (81.75–44.04)
Mononuclear cells, $x10^8$/kg	4.53 (0.91–17.30)	8.24 (1.03–27.97)
CFU-GM, $x10^4$/kg	70.60 (0.00–278.34)	27.46 (0.00–135.40)
$CD34^+$ cells, $x10^6$/kg	4.44 (0.15–42.64)	0.96 (0.03–12.50)

CFU-GM – colony-forming-units-granulocyte-macrophage

TABLE 4
THE INFLUENCE OF TOTAL NUCELATED AND MONONUCLEAR CELLS ON THE PERIPHERAL BLOOD STEM CELL COLLECTION

	Patients	Total nucleated cells, $x10^8$/kg		Mononuclear cells, $x10^8$/kg	
	N	$\overline{X}$±SD ($x10^8$/kg)*	p value	$\overline{X}$±SD ($x10^8$/kg)*	p value
Age****			0.257		0.152
0–10	1	14.89		10.98	
11–20	3	6.01±7.30		1.92±1.47	
21–30	13	8.81±6.10		5.43±4.46	
31–40	13	9.10±4.46		4.62±1.50	
41–50	26	12.93±7.44		5.35±2.88	
51–61	22	11.05±6.84		5.11±2.51	
Sex***			0.483		0.787
Male	33	11.46±7.02		5.01±2.55	
Female	45	10.37±6.49		5.19±3.27	
FAB subtype****			0.025**		0.005**
M0	3	6.43±1.97		3.13±1.76	
M1	8	7.91±3.90		4.79±2.83	
M2	34	11.24±5.35		5.00±2.29	
M3	–	–		–	
M4	9	5.70±3.42		2.89±1.05	
M5	10	13.78±8.94		6.14±3.70	
M6	3	11.90±9.34		4.95±1.26	
M7	1	4.64		2.81	
AML sec.	7	16.19±10.41		8.82±4.68	
No. of cycles of chemotherapy to CR***			0.452		0.931
1 cycle	59	10.69±6.43		5.15±2.84	
2 cycles	15	12.15±7.68		5.22±3.53	
Disease stage****			0.092		0.119
CR1	69	11.41±6.74		5.37±2.97	
CR2	3	8.61±6.61		4.47±3.75	
Relapse	3	3.07±1.87		1.79±0.54	

CR – complete remission, CR1 – first complete remission, CR2 – second complete remission *Data are computed on the basis of confidence interval 95% **Significance on the value of 0.05 ***t-test ****f-test

tients received consolidation therapy which consisted of daunorubicine, idarubicine or mitoxantrone with intermediate-doses of Ara-C; DIA (53.7%), IDIA (12.7%) and NOVIA (6.0%) (Table 2). 108 (80.6%) patients were submitted to leukapheresis. In the remaining 26 (19.4%) patients leukapheresis was not done; in 20 patients there

TABLE 5
THE INFLUENCE OF COLONY-FORMING-UNITS-GRANULOCYTE-MACROPHAGE AND CD34$^+$ CELLS ON THE PERIPHERAL BLOOD STEM CELL COLLECTION

	Patients	CFU-GM, $\times10^4$/kg		CD34$^+$ cells, $\times10^6$/kg	
	N	$\overline{X}$±SD ($\times10^8$/kg)*	p value	$\overline{X}$±SD ($\times10^8$/kg)*	p value
Age****			0.027**		0.453
0–10	1	125.40		2.71	
11–20	3	1.76±2.49		10.11±11.85	
21–30	13	59.18±53.70		6.93±11.17	
31–40	13	50.17±27.80		8.84±10.99	
41–50	26	95.56±52.19		4.52±2.62	
aauto51–61	22	95.93±72.69		5.42±3.45	
Sex***			0.592		0.114
Male	33	84.17±67.30		7.78±9.97	
Female	45	76.68±53.14		4.85±3,53	
FAB subtype****			0.074		0.730
M0	3	59.77±11.22		5.36±1.11	
M1	8	55.49±46.87		5.64±5.37	
M2	34	76.43±57.58		6.02±7.74	
M3	–	–		–	
M4	9	41.54±22.92		3.23±3.04	
M5	10	111.97±54.55		9.72±11.83	
M6	3	72.90±13.81		4.66±2.10	
M7	1	24.32		7.2	
AML sec.	7	121.65±91.34		4.39±2.49	
No. of cycles of chemotherapy to CR***			0.388		0.607
1 cycle	59	81.38±60.81		6.50±7.62	
2 cycles	15	66.58±37.43		5.42±5.59	
Disease stage****			0.196		0.710
CR1	69	83.99±59.65		6.11±7.17	
CR2	3	96.60		9.23±12.26	
Relapse	3	21.10±25.37		4.54±3.49	

CR – complete remission, CR1 – first complete remission, CR2 – second complete remission, CFU-GM – colony-forming-units-granulocyte-macrophage *Data are computed on the basis of confidence interval 95% **Significance on the value of 0.05 ***t-test ****f-test

was no increase of CD34$^+$ cells in the peripheral blood after chemotherapy, 1 patient had acute hepatitis B, 1 patient had relapse of disease, and for 4 patients there were no data. Of the total number of patients, PBSC collection was successful in 78 (58.2%) patients. As a criterion of succesful collection a total yield of $\geq2\times10^6$/kg CD34$^+$ cells was taken. Collecting was much more successful after the first attempt to mobilize HSC (Figure 1). Graft characteristics after the first and the second attempt of HSC mobilization are shown in Table 3.

115 (85.8%) patients were treated with ASCT, 71 patients (61.8%) with PBSC, 22 patients (19.1%) with BM, and 22 patients (19.1%) with PBSC and BM (Table 2). In 109 (94.8%) patients myeloablative chemotherapy consisted of busulfan and cyclophosphamide, 1 (0.9%) patient received cyclophosphamide with total-body irradiation, 2 (1.7%) patients received busulfan, cyclophosphamide and etopozide, 1 (0.9%) patient received busulfan, cyclophosphamide and idarubicine, and for 2 (1.7%) patients there were no data. Examinating the influence of the factors on the HSC collection, as shown in Tables 4 and 5, sex, number of chemotherapy cycles to achieve complete remission and stage of disease did not have a significant impact on the collection of total nucleated cells, mononuclear cells, CFU-GM and CD34$^+$ cells. Patient age had a significant impact on the collection of CFU-GM, but did not affect the collection of total nucleated cells, mononuclear cells and CD34$^+$ cells. Patients aged 21–30 and 31–40 years of age collected an average of

TABLE 6
INFLUENCE OF FACTORS ON THE COLLECTION OF $CD34^+$ CELLS AFTER THE FIRST MOBILIZATON THERAPY

	Patients	Correlation	p value
	N	r_P	
Days to WBC >1 x 10^9/L post consolidation chemotherapy	72	–0.247	0.037*
Days to harvest post consolidation therapy	69	–0.311	0.009*
WBC on the first day of harvest			
<3 x 10^9/L	14	0.543	0.178
>3 x 10^9/L	62	0.350	0.005*
Concentration of $CD34^+$ cells in peripheral blood on the first day of harvest			
<20 x 10^3/Ml	32	0.096	0.601
>20 x 10^3/Ml	34	0.854	0.000*

r_P – Pearson correlation coefficient; * Significance on the value of 0.05

TABLE 7
THE INFLUENCE OF TOTAL NUCLEATED CELLS AND MONONUCLEAR CELLS ON THE HEMATOPOIETIC RECOVERY AFTER AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION

	Patients N	Total nucleated cells		Mononuclear cells	
		Correlation coefficient r_S	p value	Correlation coefficient r_S	p-value
Days to neutrophil count >0.5 × 10^9/L	83	–0.347	0.001*	–0.131	0.237
Days to platelet count >20 × 10^9/L	52	–0.017	0.906	–0.087	0.538
No. of red blood cells units	87	–0.092	0.396	–0.066	0.542
No. of platelet units	88	–0.119	0.269	0.043	0.689
Last day of transfusion support post transplantation					
Red blood cell transfusion	81	–0.099	0.379	–0.001	0.989
Platelet transfusion	86	–0.033	0.761	0.059	0.589
No. of febrile days	87	–0.083	0.444	–0.061	0.572
No. of febrile episodes	86	–0.137	0.208	–0.082	0.453
No. of days on intravenous antibiotic treatement	85	–0.132	0.229	–0.100	0.361
Days of hospitalization	92	–0.151	0.152	0.008	0.940

r_S – Spearman correlation coefficient; * Significance on the value of 0.05

less, and patients aged 41–50 and 51–60 years of age collected an average of more CFU-GM. Subtype of AML significantly affected the collection of total nucleated cells and mononuclear cells and did not impact the collection of CFU-GM and $CD34^+$ cells. The most total nucleated and mononuclear cells were collected in patients with AML-M5 and AML-M6 and in patients with AML-M2, as well as in patients with secondary AML.

Number of days to WBC $>1\times10^9$, number of days from the start of consolidation chemotherapy to the first leukapheresis, leukocyte count in peripheral blood $>3\times10^9$/L and the concentration of $CD34^+$ cells $>20\times10^3$/mL on the first day of leukapheresis have shown significant impact on the collection of $CD34^+$ cells (Table 6).

The influence of graft composition on the hematological recovery is shown in Tables 7 and 8. Of all parameters tested, number of total nucleated cells infused had a positive influence only on neutrophil hematopoietic recovery, while the number of mononuclear cells infused did not have significant impact on hematopoietic recovery. The number of $CD34^+$ cells infused had the strongest impact on hematopoietic recovery and the number of the CFU--GM infused had a positive impact on most parameters of hematopoietic recovery. The number of $CD34^+$ cells in the graft had a positive influence on neutrophil and platelet recovery, on the number of transfused units of red blood cells and platelets, on the duration of the transfusion support and on the number of days of intravenous antibiotic therapy as well as on the length of hospitalization.

After ASCT with PBSC, when compared to BM in those patients who were not able to collect PBSC, hematopoietic recovery of neutrophils and platelets was significantly faster, number of transfused blood units was

TABLE 8
THE INFLUENCE OF COLONY-FORMING-UNITS- GRANULOCYTE-MACROPHAGE AND CD34$^+$ CELLS ON THE HEMATOPOIETIC RECOVERY AFTER AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION

	Patients N	CFU-GM		CD34$^+$ cells	
		Correlation coefficient r_S	p value	Correlation coefficient r_S	p value
Days to neutrophil count >0.5×10^9/L	80	–0.598	0.000*	–0.418	0.000*
Days to platelet count >20×10^9/L	52	–0.196	0.163	–0.275	0.049*
No. of red blood cells units	83	–0.278	0.011*	–0.402	0.000*
No. of platelet units	84	–0.422	0.000*	–0.514	0.000*
Last day of transfusion support post transplantation					
Red blood cell transfusion	78	–0.251	0.027*	–0.499	0.000*
Platelet transfusion	82	–0.354	0.001*	–0.598	0.000*
No. of febrile days	83	–0.082	0.464	–0.179	0.097
No. of febrile episodes	82	–0.162	0.147	–0.197	0.069
No. of days on intravenous antibiotic treatement	81	–0.199	0.075	–0.379	0.000*
Days of hospitalization	88	–0.445	0.000*	–0.588	0.000*

r_S – Spearman correlation coefficient, CFU-GM – colony-forming-units-granulocyte-macrophage; * Significance on the value of 0.05

lower, duration of transfusion support, intravenous antibiotic treatment and the lenght of hospitalization were shorter, while number of febrile days and febrile episodes did not differentiate after ASCT with PBCT or BM (Table 9).

Discussion and Conclusion

Although the use of PBSC for transplantation significantly increased through last 15 years, many questions in this field are still unanswered. The application of HSC in particular is little explored in patients with AML because there were doubts about their poor hematopoietic potential.

In our study CR was achieved after one cycle of induction chemotherapy in 91 (67.9%) patients with AML, which corresponds to the results of other surveys in AML patients[28–30]. In the study by Zittoun et al. CR was achieved in 576 patients (61.2%)[28]. J. Harousseau and associates included 504 patients and after induction chemotherapy achieved CR in 338 (67.1%) patients[29], and in the research by Cassileth et al. CR was achieved in 414 (56%) patients[30].

Mobilization therapy using growth factor after consolidation chemotherapy was effective in most our AML patients (58.2%) but this proportion is substantially lower in comparison to patients with lymphoproliferative diseases; non-Hodgkin lymphoma (NHL) and multiple myeloma (MM). The median number of leukapheresis procedures was 2 (range, 1–5). Failure to collect a minimum number of HSC (≥2×10^6/kg) for transplantation was previously reported in a significant number of patients (up to 40%), depending on type of disease and intensity of applied chemotherapy and radiotherapy[23]. In the work of D'Arene et al.[31] patients with various malignant diseases were included and collection was successful (≥2.5×10^6/kg) in 75% of patients. In the group of patients who did not successfully collect HSC, large proportion (41%) consisted of patients with AML. Lee et al.[32] also included patients with various malignant hematological diseases and successfully collected HSC in 71% of patients. However, they did not report results according to the type of disease. Visani et al.[33] successfully collected stem cells (≥2×10^6/kg) in 23 (79%) patients with AML, and Lee and associates[19] included 34 patients with AML and successfully collected stem cells in 33 patients. In the last two studies, sample was small and did not include patients with secondary AML as well as patients with previously diagnosed myelodisplasia which could contribute to the lower collection. Median number of CD34$^+$ cells after the first attempt to mobilize HSC in our survey (4.44×10^6/kg) is comparable to number of CD34$^+$ cells obtained in other studies.

In the study of Lee et al.[19] median number of CD34$^+$ cells in patients with AML was 4.84×10^6/kg (range 0.18–19.6). Median number of CD34$^+$ cells in HSC products in patients with various malignant hematological diseases was higher, 5.43×10^6/kg (range 0.03–60.16)[32]. In our second attempt of mobilization, success of HSC collection was poorer in comparison to the first attempt of mobilization (8.2% *vs*. 49.3%). In AML patients HSC collection is still insufficiently explored and is less efficient than in patients with other malignant diseases.

Success of mobilization is quite variable among patients, depending on certain factors such as age, the amount of previous chemotherapy and radiotherapy, type of malignant disease and degree of BM involvement with disease. Those were the factors that can affect the collection of HSC in patients with various malignant hematological diseases[13]. In general, AML is considered as a bad

TABLE 9
COMPARISON OF THE HEMATOPOIETIC RECOVERY AFTER AUTOLOGOUS TRANSPLANTATION OF BONE MARROW AND PERIPHERAL BLOOD STEM CELLS

	Patients (N)	$\overline{X}$±SE*	p value
Days to neutrophil count >0.5 x 10^9/L***			0.000**
BM	17	28.53±1.84	
PBSC	61	13,97±0.40	
Days to platelet count >20 × 10^9/L***			0.001**
BM	3	44±3.06	
PBSC	46	12.80±0.59	
No. of red blood cells units***			0.000**
BM	18	7.56±0.87	
PBSC	62	2.68±0.28	
No. of platelet units***			0.000**
BM	18	115.83±18.42	
PBSC	62	22.07±2.81	
Last day of transfusion support post transplantation***			
Red blood cell transfusion			0.000**
BM	17	36.71±3.34	
PBSC	55	10.62±1.28	
Platelet transfusion			0.000**
BM	17	45±3.63	
PBSC	60	13.90±1.22	
No. of febrile days***			0.616
BM	19	4.37±1.15	
PBSC	61	3.80±0.42	
No. of febrile episodes***			0.543
BM	19	1.16±0.12	
PBSC	60	1.07±0.07	
No. of days on intravenous antibiotic treatement***			0.000**
BM	17	21.77±3.03	
PBSC	59	13.17±0.72	
Days of hospitalization***			0.000**
BM	19	46.90±3.90	
PBSC	66	21.32±0.86	

BM – bone marrow, PBSC – peripheral blood stem cells, *Data are computed on the basis of confidence interval 95% **Significance on the value of 0.05 ***Kaplan-Meier test

prognostic factor for HSC collection, due to often resistant nature of disease, intensive cytotoxic chemotherapy and prolonged cytopenia caused by the exhaustion of hematopoietic reserves[19,34]. In this research, the collection of total nucleated cells, mononuclear cells, CFU-GM and $CD34^+$ cells was not different in patients who received one or two cycles of induction chemotherapy. Also, in other studies in AML patients, the number of cycles of induction chemotherapy to achieve complete remission or number of cycles of induction chemotherapy to HSC mobilization did not affect the collection of stem cells[19,34]. These results are different from the results in other malignant hematological diseases. Study of patients with lymphoma showed that each cycle of chemotherapy reduces the number of $CD34^+$ cells by 0.2×10^6/kg and irradiation by 1.8×10^6/kg *per* leukapheresis[35]. In the studies of patients with MM, >6 cycles of chemoterapy[36] and BM involvement with disease[37] significantly reduces the number of $CD34^+$ cells. Explanation why number of induction chemotherapy cycles does not affect the collection of HSC in patients with AML can be found in earlier observations that standard type of chemotherapy with Ara-C and antracycline, used in treatment of AML patients, has less harmful effect on normal stem cells, than, for example, alkylating agens do[38]. In addition, mobilization therapy for AML patients usually consists of 1 or 2 cycles of chemotherapy in contrast to the treatment of lymphoma patients where radiotherapy is frequently ap-

plied together with several cycles of chemotherapy (usually 6 cycles)[35]. By testing the influence of age, gender, subtype and stage of disease, we did not find a significant difference in the collection of $CD34^+$ cells. However, we demonstrated a significant impact of the subtype of disease on the collection of total nucleated and mononuclear cells and of the patient age on the collection of CFU-GM. It is the question of hematopoietic reserve in these group of patients and the mechanism by which above mentioned parameters affected the graft composition. Many studies did not find positive impact of patient age and gender on the HSC collection[19,34,35]. However, the successful collection of HSC is shown in patients with a shorter period (<2 months) from diagnosis to leukapheresis[19]. We observed successful collection of $CD34^+$ cells in patients with shorter period to harvest after the consolidation chemotherapy. Furthermore, we have shown successful collection of $CD34^+$ cells in patients with faster recovery to WBC $>1\times10^9$/L post consolidation chemotherapy. Other authors have shown the same. In the group of AML patients Jowit et al. found that shorter period to harvest HSC post consolidation chemotherapy and faster leukocyte recovery results in larger number of HSC collected[34]. Interpretation arises from an assumptions about a better reserve and hematopoietic potential of HSC in these patients. Collection of $CD34^+$ cells was also more successful in patients with faster platelet recovery post induction therapy and in patients with higher platelet number on the first day of leukapheresis ($>20\times10^9$/L), which indicates that the speed of platelet recovery is a good indicator of hematopoietic BM reserves. However, it is not proven that the speed of neutrophil recovery post induction therapy influences the collection of $CD34^+$ cells[34]. In patients with MM faster platelet recovery post chemotherapy ($>50\times10^9$/L) resulted in collection of a significantly larger number of $CD34^+$ cells[36].

Collection of a good quality graft depends on the effective mobilization of HSC and on the moment when leukapheresis starts[18]. We found a significant correlation between the number of leukocytes on the first day of leukapheresis and the success of HSC collection when the number of leukocytes was $>3\times10^9$/L. We also shoved the same positive correlation with the concentration of $CD34^+$ cells in peripheral blood of $>20\times10^3$/mL. This is in agreement with the results of other authors who have also observed that patients who have concentration of $CD34^+$ cells $>20\times10^3$/mL in peripheral blood, on the first day of leukapheresis, have a greater yield of $CD34^+$ cells in leukapheresis product in comparison to patients with a lower concentration of $CD34^+$ cells in peripheral blood[18]. Above mentioned factors however, only partially explained variability in kinetics to mobilize HSC. In healthy donors, who have normal BM function and did not receive chemotherapy, the use of G-CSF (5–16 μg/kg) also resulted in variations in collecting $CD34^+$ cells. Approximately 5–15% of healthy donors fails to collect a sufficient number of $CD34^+$ cells[10].

ASCT has to ensure complete hematopoietic and immune recovery after the application of high doses of chemotherapy[18]. The number of total nucleated cells, mononuclear cells, CFU-GM or $CD34^+$ cells has been applied as a measure of hematopoietic potential of HSC in the graft[34]. It is considered that the minimum number of 2×10^6/kg $CD34^+$ cells[4,19–33], and the optimal number of 5×10^6/kg ensures rapid hematological recovery within two weeks[18,39]. Threshold of 5×10^6 $CD34^+$ cells/kg is not absolute, and approximately half of patients who are transplanted with ≥2.5–5×10^6/kg cells, still have a quick hematological recovery. Patients who are transplanted with larger number of HSC, have faster platelet recovery[39]. With a number of $CD34^+$ cells lower than the minimum stated above, hematopoietic recovery is possibly prolonged and incomplete. After infusion $<2\times10^6$/kg $CD34^+$ cells, because of the slow hematopoietic recovery, very little or any benefits are expected from PBSC transplantation in comparison to BM. Also, HSC threshold sholud be higher for the transplantation of patients who were previously long-treated with chemotherapy. Threshold of $CD34^+$ cells that ensures rapid hematologic recovery, in patients who were treated with melphalan <6 months, is 2.5×10^6 $CD34^+$ cells/kg, while in patients who were treated with melphalan >12 months, is $>5\times10^6$/kg $CD34^+$ cells[36].

In this study we showed a significant correlation between the number of CFU-GM and $CD34^+$ cells infused and the speed of neutrophil recovery. We also showed a significant correlation between the number of $CD34^+$ cells infused and the speed of platelet recovery. Other parameters of hematologic recovery did not significantly depend on the number of CFU-GM infused. Other studies of patients with AML have shown a significant relationship between the number of CFU-GM infused and the recovery of neutrophils and platelets or between the number of $CD34^+$ cells infused and the recovery of neutrophils and platelets. After transplantation of 4.40×10^4/kg CFU-GM, the neutrophil recovery ($>0.5\times10^9$/L) was reached in 12 days and the platelet recovery ($>20\times10^9$/L) in 29 days[34]. After the transplantation of 3.51×10^6/kg $CD34^+$ cells, the neutrophil recovery was reached in 11 days and the platelet recovery in 20 days. Numbers of total nucleated cells and mononuclear cells infused do not show a significant correlation with the hematological recovery ($p=0.062$ and $p=0.701$)[19]. When evaluating total nucleated cells and mononuclear cells we demonstrated a significant correlation between the number of total nucleated cells infused and the speed of neutrophil recovery. Number of $CD34^+$ cells infused had a significant correlation with all studied parameters of hematological recovery except with the number of febrile days and febrile episodes. Today, $CD34^+$ cells and CFU-GM are applied as a replacement markers for hematopoietic stem cells[19,34].

In this study we compared hematopoietic recovery after PBSC and BM transplantation. Of note is, that our patients transplantated with BM were those who were unable to collect PBSC for transplantation. Due to small

number of data we were unable to interprete the speed of platelet recovery after PBSC and BM transplatation. In some studies median days to neutrophil recovery after PBSC transplantation or BM transplantation was 16 to 37 days and to platelet recovery 14 to 96 days, respectively[4]. In the Italian study median days to neutrophil recovery after PBSC transplantation or BM transplantation was 17 to 36 days and to platelet recovery 20 to 150 days, respectively[33]. Sirohi and associates made the same comparison and showed neutrophil recovery $>0.5\times10^9$/L in 14 and 33 days, and platelet recovery $>20\times10^9$/L in 18 and 36 days[36]. According to this, duration of transfusion support and length of hospitalization were shorter after PBSC transplantation. In the study by Visani and associates[33] duration of red blood cell transfusion support, after PBSC transplantation was 22 days in comparison to 130 days after BM transplantation and duration of platelet transfusion support was 34 and 119 days, respecitively. Accordingly, the lenght of hospitalization was 19 and 34 days, respectively. This study indicates the advantage of PBSC graft in relation to BM graft because of significantly shorter time needed for hematological recovery, lesser transfusion support with red blood cells and platelets, shorter treatment with intravenous antibiotic therapy and shorter hospitalization time. Faster hematopoietic recovery after PBSC transplantation can be explained with the transplantation of larger number of stem cells or stem cells with greater hematological potential[4]. There are other advantages of collecting PBSC: avoiding general anesthesia and the need for operating room and complications associated with BM harvesting (pain, bleeding and infections)[4]. Accordingly, TRM is reduced (1% *vs*. 5–14%)[40,41]. Therefore, application of PBSC is in patients with malignant hematological diseases justifingly increasing. Since PBSC provides faster hematopoietic recovery, treatment can be extended to a group of patients of older age[19]. In addition, PBSC transplantation significantly reduces the length of hospitalization and overall costs of treatement[39]. In AML patients, many researchers have expressed doubts about ASCT, though it is, for example, standard treatment for MM[41]. Slow hematopoietic recovery in patients with AML after BM transplantation was related to the impossibility to collect the sufficient number of HSC for transplantation or to their lower potency for hematopoietic recovery[4]. Also, there were doubts about adequacy of treating patients with AML in first remission as well as with good cytogenetic risk factors and lower risk of relapse[15]. In conclusion it can be said that the number of leukocytes $>3\times10^9$/L and the concentration of $CD34^+$ cells in the peripheral blood $>20\times10^3$/mL on the first day of leukapheresis are good indicators of effective HSC mobilization. Furthermore, as infused number of $CD34^+$ cells have the strongest influence on all parameters of hematological recovery, their number in graft is the best indicator of hematological recovery after PBSC transplantation. Likewise, hematopoietic recovery was significantly faster and the number of complications significantly lower after PBSC transplantation in relation to BM transplantation, which justifies a standard application of this method in the treatment of patients with AML. However, a lower mobilization potential in AML patients still remains a problem that needs to be resolved. Also, some studies have shown a positive impact of a larger yield of CD34+ cells on the incidence of relapse, whether the patients were transplantated or not. This observation needs further exploration and verification. Moreover, transplant type (PBSC or BM) regarding to the incidence of relapse is insufficiently explored and needs more research.

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SKUPLJANJE I SASTAV TRANSPLANTATA AUTOLOGNIH KRVOTVORNIH MATIČNIH STANICA PERIFERNE KRVI U BOLESNIKA S AKUTNOM MIJELOIČNOM LEUKEMIJOM: UTJECAJ NA HEMATOLOŠKI OPORAVAK I ISHOD

S A Ž E T A K

Transplantacija krvotvornih matičnih stanica (KMS) standardan je pristup liječenja hematoloških zloćudnih bolesti. Unazad 15 godina glavni izvor stanica za transplantaciju čine KMS periferne krvi. Dostupnošću hematopoetskih čimbenika rasta i spoznajom predosti liječenja KMS periferne krvi potisnuta je primjena koštane srži (KS). Svrha ovog rada bila je istražiti učinkovitost skupljanja KMS iz periferne krvi, čimbenike koji utječu na uspješnost skupljanja KMS iz periferne krvi, sastav i kvalitetu transplantata te njihov utjecaj na hematološki oporavak i ishod nakon liječenja transplantacijom u bolesnika s akutnom mijeloičnom leukemijom (AML). U ovom istraživanju KMS periferne krvi skupljane su postupkom leukafereze nakon kombinacije kemoterapije i faktora rasta ili samo faktora rasta. Kvaliteta pripravka KMS određena je metodom kratkotrajne kulture stanica »in vitro« i metodom protočnocitometrijske analize. Od 134 bolesnika s AML, kod kojih je učinjen pokušaj mobilizacije KMS, skupljanje je bilo uspješno kod 78 (58,2%) bolesnika. Skupljanje je bilo uspješnije nakon prvog nego nakon drugog pokušaja mobilizacije KMS (49% *vs*. 11%). Kriteriji učinkovite mobilizacije bili su broj leukocita $>3x10^9$/L i koncentracija $CD34^+$ stanica $>20x10^3$/mL u perifernoj krvi na prvi dan leukafereze. Broj infundiranih $CD34^+$ stanica imao je najjači utjecaj na hematološki oporavak. Također smo uočili značajno brži hematološki oporavak neutrofila i trombocita, manji broj transfundiranih doza koncentrata eritrocita i trombocita, brže postizanje neovisnosti o transfuzijama koncentrata eritrocita i trombocita, kraći broj dana intravenskog liječenja antibioticima i kraći boravak u bolnici nakon transplantacije KMS periferne krvi u odnosu na transplantaciju KS. Ove prednosti mogle bi osigurati njihovu standardnu primjenu u liječenju bolesnika s AML.