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Impact of stem cell source on allogeneic stem cell transplantation outcome in hematological malignancies

Uticaj izvora matičnih ćelija hematopoeze na ishod alogene transplantacije u lečenju hematoloških maligniteta

Dragana Stamatović*, Bela Balint†, Ljiljana Tukić*, Marija Elez*, Olivera Tarabar*, Milena Todorović‡, Gordana Ostojić†, Zeljka Tatomirović§, Marika Ljubenov†, Slobodan Marjanović*, Milomir Malešević*

Military Medical Academy, *Clinic of Hematology, †Institute of Transfusiology, §Institute of Pathology, **Belgrade, Serbia**; ‡**Clinical Center of Serbia**, Clinic of Hematology, **Belgrade, Serbia**

Abstract

Background/Aim. Peripheral blood (PB) is used more frequently as a source of stem cells (SCs) for allogeneic transplantation. However, the influence of cell source on the clinical outcome of SC transplantation is not yet well established. The aim of this study was to compare the results of PBSC transplantation (PBSCT) with bone marrow transplantation (BMT) on the basis of engraftment, frequency and severity of immediate (mucositis, acute Graft *versus* Host Disease – aGvHD) and delayed (chronic GvHD – cGvHD) complications, as well as transplant-related mortality (TRM), transfusion needs, relapses and overall survival (OS). **Methods**. We analyzed 158 patients, women/men ratio 64/94 median age 29 (range 9–57), who underwent allogeneic SC transplantation between 1989 and 2009. All included patients had diseases as follows: acute myeloid leukemia (AML) – 39, acute lymphoblastic leukemia (ALL) – 47, chronic myeloid leukemia (CML) – 32, myelodysplastic syndrome (MDS) – 10, Hodgkin's lymphoma (HL) – 2, multiple myeloma (MM) – 3, granulocytic sarcoma (GrSa) – 3, severe aplastic anemia (sAA) – 22. The patients underwent transplantations were divided into two groups: BMT group (74 patients) and PBSCT group (84 patients). Each recipient had HLA identical sibling donor. SCs from bone marrow were collected by multiple aspirations of iliac bone and from PB by one "Large Volume Leukapheresis" (after recombinant human granulocyte colony stimulating factor, rHuG–CSF) application (5–12 μg/kgbm, 5 days). Conditioning regimens were applied according to primary disease, GvHD prophylaxis consisted of combination of a cyclosporine A and methotrexate. **Results**. Engraftment, according to the count of polymorphonuclear and platelets, were significantly ($p < 0.001$) faster in the PBSCT *vs* BMT group. The needs for transfusion support were significantly ($p < 0.01$) higher in the BMT group. Those patients had more frequently oropharingeal mucositis grade 3/4 (33.3% *vs* 10.0%, $p < 0.05$). There were no significant differences in the incidence of aGvHD and cGvHD between the two groups. The patients who underwent PBSCT had more frequently extensive cGvHD in comparison with the BMT group (29.1% *vs* 11.29%, $p < 0.05$). SC source (SCS) had no significant influence on the TRM (21.62% *vs* 23.8%, $p = 0.64$) and the incidence of relapses (21.6% *vs* 29.7%, $p = 0.32$). Finally, the patients treated by BMT had a significantly better OS (logrank 2.33, $p < 0.05$). **Conclusion**. SCs harvesting from PB resulted in improved cell yield, faster engraftment, as well as in a decrease of immediate transplantation related complications with a reduced treatment cost. Allogeneic PBSCT were associated with more frequent extensive cGvHD, while the influence of SCS in TRM and relapses was not observed. Finally, the long-term OS was better in the patients treated by BMT. To verify impact of SC source on transplantation (PBSCT *vs* BMT) overall efficacy, more larger randomized clinical studies are needed.

Key words:
hematologic neoplasms; therapeutics; transplantation, homologous; hematopoietic stem cell transplantation; bone marrow; blood; treatment outcome.

Apstrakt

Uvod/Cilj. Periferna krv (PK) se sve češće koristi kao izvor matičnih ćelija (MĆ) hematopoeze za alogenu transplantaciju. Uprkos višegodišnjem iskustvu, uticaj izvora MĆ na ishod transplantacije u lečenju hematoloških maligniteta nije jasno definisan. Cilj rada bio je da se uporede rezultati alogenih transplantacija MĆ iz PK (TPMĆ) i transplantacija koštane srži (TKS) prema dinamici prihvatanja kalema, učestalosti i jačini ranih (mukozitis, akutna bolest „kalem protiv

Correspondence to: Dragana Stamatović, Military Medical Academy, Clinic of Hematology, Crnotravska 17, 11 000 Belgrade, Serbia; E-mail: stamatovicm@sbb.rs

domaćina", (*graft-versus-host disease* – aGvHD) i odloženih (hronični GvHD – hGvHD) komplikacija procedure, mortalitetu uzrokovanom transplantacijom (TRM), potrebi za transfuzijama, relapsima i ukupnom preživljavanju (OS). **Metode.** Analizirano je 158 bolesnika, 64 ženskog, 94 muškog pola, prosečne starosti 29 godina (9–57), sa oboljenjima: akutna mijeloidna leukemija (AML) – 39, akutna limfoblastna leukemija (ALL) – 47, hronična mijeloidna leukemija (CML) – 32, mijelodisplastični sindrom (MDS) – 10, Hodgkinova bolest (MH) – 2, multipli mijelom (MM) – 3, granulocitni sarkom (GrSa) – 3, teška aplatična anemija (sAA) – 22, kod kojih je u periodu 1989–2009. urađena alogena transplantacija MĆ. Bolesnici su prema izvoru transplantiranih MĆ bili podeljeni u dve grupe: prva grupa sa TKS – 74 i druga sa TPMĆ – 84 bolesnika. Kod svih bolesnika davalac je bio HLA podudarni srodnik. Matične ćelije iz koštane srži prikupljene su multiplim aspiracijama bedrene kosti, a iz periferne krvi jednom „aferezom velikog volumena" posle primene rekombinantnog faktora koji stimuliše ljudske kolonije (rHuG–CSF, 5–12 μg/kgtm, 5 dana). Svi bolesnici primili su neselektovanu suspenziju MĆ. Kondicioni režimi bili su prilagođeni bolestima, a prevencija GvHD bila je kombinacija ciklosporina A i metotreksata. **Rezultati**. Prihvatanje kalema, prema broju polimorfonukleara i trombocita bilo je značajno brže ($p < 0,001$) u grupi bolesnika sa TPMĆ, nego u grupi sa TKS. Potrebe za transfuzijama bile su značajno veće u grupi bolesnika sa TKS ($p < 0,01$). Ovi bolesnici imali su češće orofaringealni mukozitis stepena 3/4 (33,3% *vs* 10,0%, $p < 0,05$). Nije bilo značajne razlike u učestalosti aGvHD i hGvHD među grupama. Bolesnici sa TPMĆ imali su značajno češći hGvHD ekstenzivne forme (29,1% *vs* 11,29%, $p < 0,05$). Izvor MĆ nije bitnije uticao na TRM (21,62% *vs* 23,8%, I= 0 ,64) i relapse (21,6% *vs* 29,7%, $p = 0,32$). Bolesnici sa TKS imali su značajno bolje OS (*log-rank* 2,33; $p < 0,05$). **Zaključak**. Periferna krv kao izvor obezbedila je veći prinos ćelija i brže prihvatanje kalema, sa ređim ranim komplikacijama transplantacije, što je uticalo na ekonomski aspekt lečenja. Alogene TPMĆ bile su praćene češćom pojavom ekstenzivne forme hGvHD, dok uticaj izvora MĆ na TRM i relaps bolesti nije utvrđen. Ukupno preživljavanje bilo je bolje kod bolesnika lečenih primenom TKS, ali za definitivno zaključivanje potrebno je randomizirano ispitivanje većeg broja ispitanika.

Ključne reči:
hematološke neoplazme; lečenje; transplantacija, homologna; transplantacija hematopoeznih matičnih ćelija; kostna srž; krv; lečenje, ishod.

Introduction

Allogeneic type of stem cell (SC) transplantation is the best therapeutic option for the treatment of inherited, and some acquired diseases of hematopoietic system and various hematological malignancies. Hematopoietic SC could be collected either from the bone marrow (BM) which is their natural residence or from the peripheral blood (PB) after chemotherapy and/or recombinant hematopoietic growth factors, as well as from the umbilical blood. Since 1995, PB has been almost a unique SC source (SCS) within autologous setting. Knowledge that PB has significantly higher number of immunocompetent cells, basically T lymphocytes, that could cause strong „Graft versus Leukemia" effect and the fact that the use of recombinant human granulocyte colony stimulating factor (rHuG–CSF) is harmless for donor [1], has led to more frequent use of this particular SCS in transplant procedures. According to the European Group for Bone Marrow and Blood Transplantation (EBMT), from a total number of allogeneic SCT in 2007, even 75% represents those with the SCS from the peripheral blood [2]. The results of allogeneic PB SC transplantation (PBSCT) were compared with the allogeneic BM transplantation (BMT) for the treatment of hematologic malignancies. Allogeneic PBSCT is followed with faster engraftment as compariset with BMT and therefore with a reduced amount of early complications related to the period of iatrogenic myelosuppression, such as mucositis and some types of infections [3–8]. There are two different types of graft *versus* host disease (GVHD); acute GVHD (aGVHD) and chronic GVHD (cGVHD). The majority of authors [5, 6] have citated that PBSCT is followed with higher risk of appearance of cGvHD [5, 6], while reports on the impact of SCSs on the frequency and severity of aGvHD are controversial [7, 9–11].

Until nowadays, there has been no consensus between investigators on the influence of SC source on the disease relapse, transplant related mortality (TRM) and overall survival (OS). According to the majority of them, there is no significant impact of SCS on relapses, TRM and OS [6, 12]. There are some study groups that emphasize that allogeneic PBSCT in adults, especially in the cases of advanced stages of leukemia, has less TRM and better OS in comparison with allogeneic BMT [7, 8, 13–15].

The aim of this retrospective study was to compare PBSCT with BMT considering the engraftment, frequency and severity of immediate (mucositis, aGvHD) and delayed (cGvHD) complications, relapses TRM, and OS.

Methods

We analyzed the data on 158 patients, 64 women, 94 men median age 29 years (range 9–57), with different hematological diseases: acute myeloid leukemia (AML) – 39, acute lymphoblastic leukemia (ALL) – 47, chronic myeloid leukemia (CML) – 32, myelodysplastic syndrome (MDS) – 10, Hodgkin's lymphoma (HL) – 2, multiple myeloma (MM) – 3, granolocytic sarcoma (GrSa) – 3, severe aplastic anemia (SAA) – 22) who underwent allogeneic SC transplantation in our center from 1989 till 2009 (20 years of follow up) (Table 1).

The patients were divided into two groups according to SC source: in the first group (BMT) the SC source was BM – 74 patients (AML – 17, ALL – 13, CML – 20, MDS – 2, MM – 1, GrSa – 1, SAA – 20) and in the second group (PBSCT) SCs which originate in PB – 84 patients (AML – 22, ALL – 34, CML – 12, MDS – 8, HL – 2, MM – 2, GrSa – 2, SAA–2) (Table 2).

Table 1

Clinical characteristics of the patients before the stem cell transplantation (n = 158)

Parameter	Values
Average age (age range), (years)	29 (9–57)
Women/men ratio (n)	64/94
Diagnosis (n)	
severe aplastic anemia	22
chronic myeloid leukemia	32
chronic phase	27
acceleration/ blast crisis	3/2
Acute myeloid leukemia (n)	39
CR1*	36
CR2**	3
Acute lymphoblastic leukemia (n)	47
CR1	28
CR2	11
resistant disease	8
Myelodysplastic syndrome (n)	10
Hodgkin lymphoma (n)	2
Multiple myeloma (n)	3
Granulocytic sarcoma (n)	3
Type of donor (n)	
singeneic	5
HLA identical sibling	146
HLA mismatched	5
haploidentical	2
Sources of stem cell (n)	
bone marrow	74
peripheral blood	84
Conditioning regimen (n)	
busulfan and cyclophosphamide	114
cyclophosphamide + antitbymocyte globulin	22
other	22
Graft versus host disease prophylaxis (n)	
cyclosporine A + metotrexate	130
other	28

***CR1– first complete remission; **CR2 – second complete remission**

Table 2

Clinical characteristics of 158 patients according to the stem cell source

Parameter	Group of patients	
	BMT (n = 74)	PBSCT (n = 84)
Average age (age range), (years)	26 (9–52)	28 (13–57)
Diagnosis (n)		
severe aplastic anemia	20	2
chronic myeloid leukemia	20	12
acute myeloid leukemia	17	22
acute lymphoblastic leukemia	13	34
myelodysplastic syndrome	2	8
hodgkin lymphoma	0	2
multiple myeloma	1	2
granulocytic sarcoma	1	2

BMT – bone marrow transplantation; PBSCT – peripheral blood stem cell transplantation

Each patient had a HLA sibling donor. Five of them were syngeneic SC transplanted, 146 fully matched, 5 HLA mismatched and 2 were haploidentical. SCs from the BM were collected in the standard way, in the conditions of total anesthesia, by multiple needle aspiration from the donor iliac crest up to 15 mL/kgbm. SCs from the PB were usually collected, after an with apheresis of "large volume" that followed previous mobilization rHuG–CSF, 5–12 μg/kgbm for 5 consecutive days. All the patients received unselected suspension of SCs and in the cases of recipient–donor ABO incompatibility, adequate pre-and peritransplant preparation were performed.

Conditioning regimens were adjusted to the primary diseases. In the cases of acute leukemias, CML and GrSa combination of busulfan and cyclophosphamide 2 (Bu–Cy2) with or without addition of idarubicine (IDA) was given, whilst in MM Bu–Cy2+Melphalane was given. Conditioning in SAA was consisted of cyclophosphamide and antithymocyte globulin (Cy+ATG). Most of the used prevention of GvHD included combination of cyclosporine A and metho-

trexate (CsA+MTX) – "short" Seattle regimen [16]. In the posttransplant period, the patients received antimicrobial prophylaxis against possible infections (viral, fungal, bacterial, *Pneumocystis jiroveci*) along with the applications of intravenous immunoglobulins until the reconstitution of the immune system. All blood products were irradiated and filtrated. Engraftment is defined as the recovery of polymorphonuclears (PMNs) above 0.5×10^9/L and platelets (Plt) over 20×10^9/L in three consecutive days. BM analyses were done on the days +14 and +28 after SC transplantation and chimerism was estimated with the available methods (sex chromosome, cytogenetic marker of disease, red blood cells phenotype, DNA isolation) starting from day +40 and afterwards in three months following SC transplantation. Grading of aGvHD was according to the approved "consensus" criteria [17]. All the patients who were alive at least 90 days after SC transplantation with adequate engraftment were enrolled in the analysis for cGvHD. TRM is defined as death after SC transplantation, while relapse is not included as a possible cause.

For comparison of the existence of some variables between the groups the χ^2 test was used. The analysis with the OS were evaluated with Kaplan–Meier method and Mann, Whitney test, were evaluated. The differences were considered as statistically significant at p values less than 0.05.

Results

The patients with PBSCT received much better specimen (sample) of mononuclear cells (MNC) ($10.07 \pm 7.31 \times 10^8$ *vs* $2.33 \pm 0.79 \times 10^8$, $p < 0.001$) in comparison with BMT. Engraftment, according to the number of PMN ($> 0.5 \times 10^9$/L) and Plt ($> 20 \times 10^9$/L) were significantly faster ($p < 0.001$) in the group of the patients treated with PBSCT for 6 days (Table 3). Needs for transfusion support of blood products (red blood cells – RBC, and Plt) were significantly higher in the BMT group ($p < 0.01$). The patients with BMT had more frequently oropharingeal mucositis grade 3–4 (33.33% *vs* 9.5%, $p < 0.05$) in comparison with the other group (Table 3). There were no significant difference between the two groups according to the incidence of aGvHD (47.3% *vs* 45.2%, $p = 0.92$). The patients with PBSCT had more often advanced form of aGvHD (3–4) but not at a significant level (4.05% *vs* 14.2%, $p = 0.055$). Although between the compared groups (BMT *vs* PBSCT) there were no differences in the incidence of cGvHD (37.1% *vs* 49.1%, $p = 0.16$), extensive form of cGvHD was significantly more frequent in the group with SCs originated from PB (11.29% *vs* 29.16%, $p < 0.05$). We did not notice significant differences in the incidence of relapses (21.6% *vs* 29.7%, $p = 0.32$) and TRM (21.62% *vs* 23.8%, $p = 0.64$) between the two groups of patients (Table 3).

The patients with BMT had significantly better OS in comparison with the other group (log–rank 2.33, $p < 0.05$, with median survival (X) 50.72 ± 65.79 months, $p < 0.05$) (Figure 1).

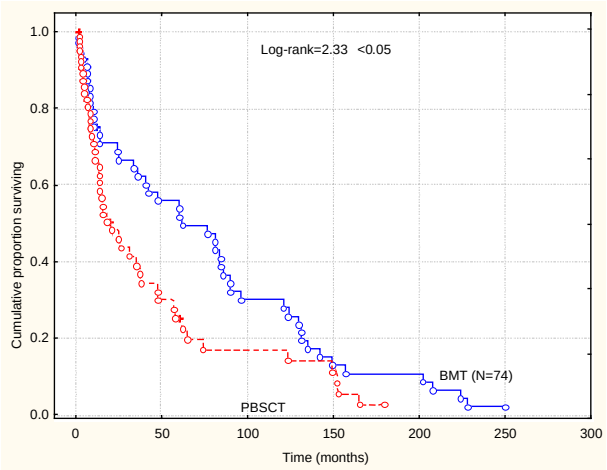

Fig. 1 – Overall survival in the 158 patients regarding the stem cell source
BMT – bone marrow transplantation; PBSCT – peripheral blood stem cell transplantation

Furthermore, among the isolated, homogenous groups of patients concerning primary disease (AML – totally 39, BMT– 17, PBSCT – 22), the results were similar (Table 4).

Table 3

Results of stem cell transplantation in all patients according to the number of mononuclear cells (MNC), polymorphonuclears (PMN), platelet (Plt), needs for red blood cells (RBC) transfusions acute and chronic graft-*versus*-host disease (GvHD) and mucositis accurrence, transplant-related mortality (TRM) and relapses

Parameter	Group of patients		*p*
	BMT (n = 74)	PBSCT (n = 84)	
MNC $\times 10^8$/kg bm	2.33 ± 0.79	10.07 ± 7.31	< 0.001
PMN > 0.5×10^9/L (days)	17.19 ± 5.65	11.06 ± 1.92	< 0.001
Plt > 20×10^9/L (days)	21.31 ± 5.46	15.35 ± 2.44	< 0.001
RBC transfusions (n)	4.0 (2–16)	2.0 (1–23)	< 0.01
Plt transfusions (n)	3.0 (1–8)	1.0 (0–16)	< 0.01
Mucositis grade 3–4 (%)	33.33	9.5	< 0.05
Acute GvHD (%)	47.32	45.26	≅ 0.92
grade 3–4	4.05	14.29	< 0.05
Chronic GvHD (%)	37.16	49.16	≅ 0.16
limited	25.87	20.00	≅ 0.92
extensive	11.29	29.16	< 0.05
TRM (%)	21.62	23.8	≅ 0.69
Relapses (%)	21.6	29.7	≅ 0.32

BMT – bone marrow transplantation; PBSCT – peripheral blood stem cell transplantation

Table 4

Results of stem cell transplantation in the homogenous group of 39 patients with acute myeloid leukemia

Parameter	Group of patients		*p*
	BMT (n = 17)	PBSCT (n = 22)	
Acute GvHD (%)	41.17	40.90	≅ 0.75
grade 3–4	11.76	27.2	≅ 0.43
Chronic GvHD (%)	25	50	≅ 0.23
limited	18.78	10	≅ 0.38
extensive	6.22	40	< 0.05
TRM (%)	17.6	13.6	≅ 0.91
Relapses (%)	17.6	9.1	≅ 0.75

BMT – bone marrow transplantation; PBSCT – peripheral blood stem cell transplantation; GvHD – graft *versus* host disease; TRM – transplant-related mortality

The compared groups (BMT vs. PBSCT) were not different in the incidence of aGvHD (41.17% *vs* 40.9%, $p = 0.75$) and aGvHD grade 3–4 (11.76% *vs* 27.21%, $p = 0.43$). Also, there was no significant difference in the incidence of cGvHD (25% *vs* 50%, $p = 0.23$). Extensive form of cGvHD was more frequent in the group of patients treated with PBSCT (6.2% *vs* 40.0%, $p < 0.05$). According to TRM and relapses, there were no significant differences between those two groups of patients (17.6% *vs* 13, 6%, $p = 0.91$), (17.6% *vs* 9.1%, $p = 0.75$), respectively. The patients who underwent BMT had the better OS than those in the PBSCT group (log–rank 3.4, $p < 0.01$) (Figure 2).

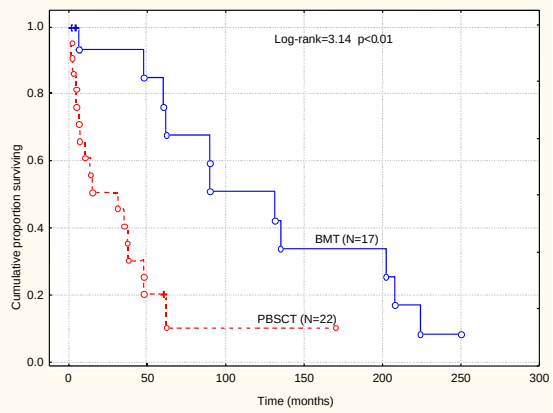

Fig. 2 – Overall survival in the 39 patients with acute myeloid leukemia regarding the stem cell source
BMT – bone marrow transplantation; PBSCT – peripheral blood stem cell transplantation

Discussion

Hematopoietic SC, used for the reconstitution of lymphohematopoiesis after the myeloablative chemo- or radiotherapy, could be received from four different sources: BM, PB, umbilical blood and rarely from the fetal liver. SCSs, among other, differ in their reconstitution and immunological characteristics which are determined by their cell structure. In "steady state" conditions in the circulation there is around 0.06% CD34+ cells, while their number is 18 times higher in the BM (1.1%) [18, 19]. After the use of recombinant hematopoietic growth factors (predominantly rHuG–CSF), SCs from the extravascular compartment of BM are migrating to the circulation. Such knowledge is a basis for the use of PB as a SCS in transplant hematology. A cell structure of unselected suspension of SCs from PB and BM is significantly different [19]. Following mobilization with addition of rHuG–CSF allograft that origins from PB consists of 2 to 4 times higher number of CD34+ cells, even 10 times higher number of T lymphocytes, monocytes and natural killer (NK) cells than allograft from BM [19, 20]. Concerning such findings, it is clear that investigations of many study groups [3–6], the same as ours, consider that PBSCT is followed with a significantly faster engraftment as compared with BMT. Faster engraftment influences on shortening of duration of iatrogenic BM aplasia and thus in the case of PBSCT, there is a significantly less need for transfusion support (RBC, Plt) and immediate complications of procedure are very rare (oropharingeal mucositis). From this point of view, our results are compatible with the mentioned facts.

As concerning the frequency and severity of aGvHD in BMT and PBSCT, reports are rather controversial. Initially, such as the EBMT analysis published, significantly much frequent appearance of aGvHD in the cases of PBSCT were registrated [6], which is due to the activity of a large number of allogeneic immunocompetent cells that are infused through this particular procedure. That was showed in addition in the course of two other meta-analyses [9, 15]. Such findings were not approved in other studies with no significant difference in the incidence of aGvHD between those two groups [5, 11]. Application of rHuG–CSF within the mobilization process, results in immunomodulatory effect among cells in the allograft suspension, with the majority of suppressive Th2 cytokines and consecutively reduction of aGvHD frequency, despite a large number of infused T lymphocytes [9].

In our clinical study, similarly to the previous reports, we noticed no difference in the frequency of aGvHD between the two compared groups, although the patients with PBSCT had more commonly advanced forms of aGvHD, but without a statistical significance.

Considering impact of SCS on the frequency of cGvHD, the majority of reports emphasized that PBSCT is followed with higher risk for the development of cGvHD, especially an extensive form [5, 6, 9, 11, 15, 21] and we came to the same conclusion within our group of patients. But, there are some opposite attitudes, according to which SCS does not have any significant influence on the severity and frequency of cGvHD [22]. A complete difference in those two findings could be caused by various factors, such as: insufficiency of statistical methods, small number of tested patients, the pres-

ence of unhomogenuos groups of patients considering primary disease, follows-up in less than 100 days after transplant, *in vivo* immunomodulatory effect of posttransplant use rHuG–CSF, etc [23]. Also, it should be kept in mind the fact that usually there is no consensus an the exact diagnosis and grading of cGvHD.

Recent studies are not unified in defining impact of SCSs on the incidence of relapses, OS and TRM. The presence of cGvHD could be, according to theoretical knowledge, followed with potential graft *versus* leukemia effect with better control of minimal residual disease and thus fewer rates of relapses and also better OS. Also, the existence of extensive form of cGvHD is followed with higher risk for TRM. Despite the relevant theoretical knowledge, most studies approved no significant difference in the incidence of relapses, TRM and OS between PBSCT and BMT [6, 12, 15, 24]. Some reports emphasize that PBSCT is useful in advanced stages of CML (acceleration and blast crisis) and acute leukemias, with lower relapses and better OS [7, 13, 14, 25]. In our investigation, we noticed no significant difference in the incidence of relapses and TRM considering SCS, neither in the whole group of patients (N = 158), nor in the homogenous group with AML. Nevertheless, the patients who underwent BMT (the whole group and the homogenous group with AML) had significantly better OS as compared to the patients who received PBSCT. The fact that the patients with PBSCT had more frequently, potentially fatal, extensive form of cGvHD could be the reason for such finding.

The results of this retrospective analysis are in accordance with findings from other studies. PB, as a source of SC, gives larger harvest of MNC and thus higher number of hematopoietic progenitor cells that lead to faster engraftment. Faster engraftment is followed by less immediate complications of the transplant procedure (infection, mucositis) and in that way, economic aspect is better (lower need for transfusion support and antibiotics, shorter hospitalization). The patients who underwent PBSCT more frequently had extensive, potentially fatal, form of cGvHD having bad impact on their quality of life. There was no difference in the frequency of aGvHD, incidence of relapses and TRM between the two groups concerning SCS. OS was better in the group with BMT due to a potentially fatal outcome of the cGvHD in PBSCT setting.

Conclusion

The data obtained in this clinical study show that the cell yield is higher in PB harvest, that engraftment is faster, with decreased immediate transplantation-related complications in PBSCT setting. For the advanced stage of acute leukemias and accelerated CML or CML with blast crisis, as well as in the ABO incompatible transplantations or a significant difference in donor *vs* recipient body mass, PB is a more sufficient SCS. However, allogeneic PBSCT is associated with more frequent extensive cGvHD, but without influence on the TRM and relapses. On the contrary, BM is superior for SAA and chronic phase of CML. To confirm the influence of SCS on the overall treatment efficacy (PBSCT *vs* BMT), more larger randomized clinical studies are needed.

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