

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Hematopoietic Stem Cell Source and Storage

Sinem Civriz Bozdag and Osman İlhan

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/60994>

Abstract

Hematopoietic stem cell transplantation (HSCT), has been accepted as a feasible treatment option that prolongs survival in hematological malignancies. Stem cell choice during hematopoietic stem cell transplantation can differ according to the experience of physicians, mostly treated hematological diseases in the centers or ongoing clinical trials. In this chapter we will discuss the advantages and disadvantages of three stem cell sources peripheral blood, bone marrow and umbilical cord blood.

Keywords: hematopoietic stem cell

1. Introduction

Hematopoietic stem cell transplantation (HSCT) has been accepted as a feasible treatment option that prolongs survival in hematological malignancies. Bone marrow (BM) has been widely used as stem cell source in the early stem cell transplantation series. Tendency towards peripheral blood (PB) as stem cell source has been started in the beginning of 2000s. Initially, advantages of peripheral blood stem cell collection have been demonstrated in autologous stem cell transplantation (autoSCT). The introduction of peripheral blood into allogeneic stem cell transplantation (alloSCT) has been followed by allogeneic transplantation from unrelated donors. Due to the less stringent HLA matching requirement, cord blood stands out as an option for patients who do not have HLA-matched donors.

Stem cell choice can change according to the experience of physicians, mostly treated hematological diseases in the centers or ongoing clinical trials. In this chapter, we will discuss the

advantages and disadvantages of three stem cell sources: peripheral blood, bone marrow, and umbilical cord blood.

2. Peripheral blood versus bone marrow

Although the early transplantation series mostly used bone marrow as stem cell source, the administration of granulocyte colony-stimulating factor allowed physicians to collect stem cells from peripheral blood by apheresis procedure. Studies in autologous stem cell transplantation (autoSCT) have been reported first. Faucher et al. [1,2] compared peripheral blood and bone marrow in a series with small patient numbers and reported an improvement in hematological recovery and a decrease in hospitalization duration. Survival of the patients was found to be similar between these two stem cell sources [3]. Also, the cost-effectiveness of the procedure increased peripheral blood stem cell transplantation rates compared with bone marrow transplantation. In a study, the total cost in peripheral blood stem cell transplantation was found to be 27.5% less than bone marrow transplantation. Faster hematological recovery, fewer hospitalization days, and less antibiotic treatment created this difference in total cost [4].

Afterwards, the comparison of peripheral blood with bone marrow in allogeneic stem cell transplantation (alloSCT) setting was started. Bensinger et al. [5] reported faster hematological recovery, less transfusion numbers, less severe acute graft versus host disease (a gvhd in favor of PB), but similar chronic graft versus host disease (cGVHD) rates. Our centers' experience also revealed faster engraftment, fewer transfusions with PB [6]. Mifflin et al. [7] showed that increasing the infused CD34+ cell number over $4 \times 10^6/\text{kg}$ can significantly accelerate the engraftment kinetics.

In a multicenter randomized trial performed by the European Group for Blood and Marrow Transplantation (EBMT), transplant-related mortality and leukemia-free survival rates showed no significant difference between PB and BM [8]. Mielcarek et al. [9] reported a better 10 years disease-free survival in favor of PB but similar overall survival between two stem cell sources. In a Cochrane database review, trials including related stem cell donors were analyzed. Both neutrophil and platelet recoveries were faster in PB. Disease-free survival, nonrelapse mortality was not different between PB and BM. The advantage of relapse in PB was recorded [10].

Peripheral blood has more CD34+ cells but has also more T cells in comparison with BM. This reflects to the outcomes as more acute and chronic GVHD rates. In a study, acute grades I–IV GVHD incidences for infused CD34+ cell doses less than $2 \times 10^6/\text{kg}$, between $2 \times 10^6/\text{kg}$ and $4 \times 10^6/\text{kg}$, and more than $4 \times 10^6/\text{kg}$ were 21%, 35%, and 43%, respectively. In the same study, increase in CD3+ cell dose was also identified as an independent factor for acute GVHD [11]. The correlation between infused cell dose and chronic GVHD has also been shown. Zaucha et al. reported CD34+ cell doses over $8 \times 10^6/\text{kg}$ were found to be associated with increased clinical extensive chronic GVHD. However, this association could not be shown with stem cell transplantation from bone marrow [12]. cGVHD after PB transplantation has to be treated for

a longer period with higher immunosuppressive regimens. The presence of cGVHD has been found to be related with fewer relapses but more treatment-related mortality [13–16].

The comparison of stem cell sources has been performed according to the diagnosis of hematological malignancies. Pidala et al. [17] performed a Markov model in which PB was found to be the optimum stem cell source for hematological malignancies, which had an advantage of 7 months in comparison with BM. BM was chosen to be superior in patients with 1-year relapse rates lower than 0.05. Patients with high-risk hematological malignancies like acute leukemia in second or later remission, chronic myeloid leukemia (CML) in blastic transformation, refractory anemia with excess blast in transformation, and heavily pretreated lymphoma patients were found to benefit from PB transplants in comparison with BM transplants [16]. A meta-analysis of nine randomized clinical trials showed better disease-free and overall survival with PB in late stage disease [18]. In a randomized study of patients with myeloid malignancies, acute myeloid leukemia AML, CML and myelodysplastic syndrome (MDS), hematological recovery was faster in PB group. Improvement in overall survival with PB was found to be related with reduction in nonrelapse deaths, with no difference in early, late relapses, or deaths in relapses [19]. In another study, which has included chronic myeloid leukemia patients, the incidence of acute and extensive chronic GVHD was similar between BM and PB patients, and there was no significant difference between survival and nonrelapse mortality rates. However, in the subgroup analysis of chronic phase patients, PB patients experienced more chronic GVHD, and BM patients had higher relapse rates [20]. The advantage of BM remains in benign hematological diseases, where chronic GVHD rates affect transplant outcomes negatively. In a study that included 537 adolescent aplastic anemia patients who had alloSCT, the survival advantage for BM recipients was reported to be significant [21]. Bacigalupo et al. [22] showed the advantage of BM also for the patients older than 50 years. The major causes of death were GVHD, infections, and graft rejection in this study. GCSF-stimulated and GCSF-unstimulated bone marrow and peripheral blood have been compared in another study that included aplastic anemia patients. Engraftment rates were not different in three treatment arms. Grades II–IV acute GVHD and chronic GVHD rates were higher with PB transplants in comparison with BM. GCSF-manipulated BM was not superior to BM in terms of mortality rates [23].

Late effects of transplantation were also analyzed in studies. Performance status, return to work, incidence of bronchiolitis obliterans, and hematopoietic functions were found to be similar between PB and BM. Also, there was no significant difference in secondary malignancies between the groups [24].

As HLA-matched siblings can be found in 25% of the patients, either PB or BM of the unrelated donors has been accepted as sources for stem cell transplantation. Eapen et al [25] reported significantly higher acute and chronic GVHD risk but similar transplant-related mortality and survival rates with PB than BM in unrelated allogeneic stem cell transplants. In a phase 3, multicenter randomized trial from 46 transplant centers in the United States and Canada, only chronic GVHD rates were significantly higher in PB transplantations. In long-term outcome analysis, chronic GVHD was graded as extensive in 85% of PB recipients compared with 76% of BM recipients. Neutrophil and platelet engraftment rates were found to be significantly

higher in PB transplantations, but no difference was observed in survival outcomes [26]. In a Cochrane database review, trials including unrelated stem cell donors were also revised. Both neutrophil and platelet recovery was faster in PB transplantations. Disease-free survival, nonrelapse mortality of PB, and BM recipients were not different. The relapse advantage of PB was not proved. Acute grades II–IV incidence did not reveal a statistical significance, whereas extensive chronic GVHD rates were in favor of BM [10].

The outcomes of unrelated allogeneic stem cell transplantation were also separately assessed according to the diagnosis of hematological diseases. During an overall survival of 7 years, nonrelapse mortality and relapse rates were similar in acute myeloid leukemia and myelodysplastic syndrome patients who have received PB or BM. The only significant difference was reported in chronic myeloid leukemia patients due to higher nonrelapse mortality rates in PB transplants [27]. In a Korean study, the difference in GVHD incidence could be overcome by risk adapted GVHD prophylaxis in AML patients [28]. In aplastic anemia patients, the risk of death was higher with unrelated donors, but peripheral blood as a stem cell source was a negative predictor for outcomes [29].

The impact of conditioning regimens in unrelated allogeneic stem cell transplantation has also been assessed in clinical trials. EBMT data showed that when reduced intensity conditioning (RIC) regimens were used in unrelated transplant settings, acute and chronic GVHD rates were higher, and relapse rates were lower in PB transplants of AML patients [30]. In contradictory with these results, GVHD, relapse, and survival rates of hematological malignancies who had unrelated stem cell transplantation were reported to be similar in a recent trial [31].

The issues that have to be paid importance during hematopoietic stem cell transplantation should be the benefits of either the donor or the patient.

Both the peripheral blood and the bone marrow have advantages and disadvantages for the donors. Peripheral blood donation is a collection of HSC from peripheral blood after a 5-day course of granulocyte colony-stimulating factor administration on 1–2 days via 4–5 hours of apheresis procedure. The monitorization of circulating CD34+ cells on the first day of apheresis is predictive for stem cell yield [32].

Peripheral blood stem cell collection seems to be an easier collection method, but the central venous line can be a necessity for some of the donors if the standard peripheral venous line is not adequate. Again in NMDP experience, femoral and jugular lines were in same frequency, which was twice as the subclavian line [33]. The collection of peripheral blood stem cells via apheresis procedure has been proven to be an effective and safe method for donors [34]. Bone marrow harvesting is the collection of HSC from posterior iliac crest under anesthesia. Hospital admission can be necessary for postoperative follow-up. In a prospective study, the experience of donors for bone marrow and peripheral blood collection has been compared. Bone marrow donors were found to be less confused and more prepared for donation. They also found the process psychologically beneficial in a short term. However, the long-term health-related quality was similar between both donors [35]. In a survey of 51,024 AHSCT performed by 338 teams, five donor fatalities were observed. Severe adverse events were reported in 37 donors. Hematological malignancy rates were not different from the age and sex-adjusted general

population [36]. Bone pain was the most frequent side effect of donors; in bone marrow donors, pain at the collection site and in peripheral blood donors pain at various sites of body during GCSF administration have been reported. Tiredness, light-headedness, nausea, sleeping problems, and chills were the other frequent side effects. At 12 months postdonation, the most common side effects were tiredness and muscle aches [35]. A median time to recovery in PB and BM donors were 1 and 2 weeks, respectively [37]. In a prospective trial from NMDP, females and heavier donors had more III–IV CALGB adverse events [38].

3. Umbilical cord blood

Umbilical cord remains to be a stem cell source option for patients who do not have a matched sibling or unrelated donor. The first umbilical cord blood transplantation has been performed at the end of the 1980s in a child diagnosed with Fanconi anemia [39]. Today, the storage of more than 600,000 cryopreserved cord bloods serves as an alternative option for both pediatric and adult patients. In the U.S. registry, almost all of the patients younger than 20 years and 80% of the patients older than 20 years had cord blood mismatched units in one or two HLA locus [40].

Rapid availability, no requirement for full HLA match, and being an option for ethnic minorities became the advantages of umbilical cord. Also, no harm for donor can be another important feature in stem cell source choice. Lack of sufficient cell doses for adult patients, delayed engraftment, poor immune reconstitution, and high infection rates are the major disadvantages of cord blood transplantation. Cord blood includes more naive T cells and Tregs. The first naive T cells proliferate but show a limited repertoire. Then a thymic-dependent population expands, which can be affected by conditioning regimen, GVHD, or aging [41].

The standard practice for the HLA typing of cord blood units is to analyze A-B antigens and DRB1 alleles with high resolution. The acceptable HLA match is 4 to 6/6 match for performing transplantation, but each mismatch results in increased TRM, increased severity of acute GVHD, and decreased survival [42]. Eapen et al. [43] reported the impact of level matching on TRM and neutrophil engraftment. Neutrophil recovery was found to be delayed in transplantations with more than two mismatches, and nonrelapse mortality was reported to be higher in 1–5 mismatch compared with HLA full-match transplantations. HLA C matching has also been shown to be beneficial in studies [42,44]. Barker et al. [45] analyzed 1691 MDS and AML patients who received single cord blood transplantation and found that regardless of cell dose, HLA A, B, and DR-matched transplantations result in the best outcomes. Total nucleated cell (TNC) doses greater than $2.5 \times 10^7/\text{kg}$ in one mismatch recipient and $5 \times 10^7/\text{kg}$ in two mismatch recipients have been shown to be sufficient for better survival. In another study, high-resolution DRB1 match was related with less acute GVHD and better event-free survival rates. Also, in the same study, infusing higher CD34⁺ cells, CD34⁺HLA DR⁺ CD38⁺ cells, and CD3⁺ cells resulted in faster engraftment [46]. The impact of HLA mismatch direction between donor and recipient has also been assessed by EUROCORD/EBMT analysis. Neither one to two mismatch in graft versus host direction nor host versus graft direction was found to be related with increased nonrelapse mortality and survival [47].

Graft failure risk remains to be a problem in 10%–20% of patients who had cord blood transplantation [48]. Neutrophil and platelet engraftment is delayed in cord blood transplantations. Engraftment is shown to correlate with cell dose infused [49]. In an analysis of 1268 patients with acute leukemia, 3 years overall survival was 47% and TRM was 16%. Delay in engraftment was associated with increased mortality and shorter survival rates [50].

Survival outcomes have been improved over years with better patient, conditioning regimen selection, and progress in HLA typing [44]. Rubinstein et al. [51] showed that 46% of the patients experienced transplant-related events by posttransplant day 100. Transplant-related events and event-free survival were related with diagnosis, number of leukocytes in the transplant, age, extent of HLA disparity, and transplant center. Cohen et al. [52] reported the outcome of 500 patients who had single-unit cord blood transplantation from 1995 to 2005 and found 1 year survival as 37%. Factors affecting early mortality following the myeloablative single-unit cord blood transplantation were cell dose, advanced disease, older age, cytomegalovirus status, female gender, and limited cord blood center experience. A Japanese study revealed that disease status and cytogenetics had an impact on event-free survival rates in AML patients [53]. For acute lymphoblastic leukemia patients who had cord blood transplantation, the factors associated with better leukemia-free survival were age, advanced disease, and conditioning regimen [54]. Brunstein et al. [55] reported 3 years event-free and overall survival as 38% and 45%, respectively, by performing transplantation with nonmyeloablative conditioning. In a comparative study, on the effect of conditioning regimen intensity, transplant-related mortality was similar with both regimens; lower risk of relapse and longer leukemia-free survival could be achieved after myeloablative regimens [56]. Fludarabine in combination with total body irradiation (TBI) concluded with high treatment-related mortality [57]. In another trial, fludarabine, TBI in combination with busulphan versus cyclophosphamide has been investigated; cyclophosphamide resulted in better transplantation outcome [58]. Also, the Japanese group used a myeloablative conditioning regimen, which included TBI, cytarabine, and cyclophosphamide, and reported 51% overall survival for high-risk hematological malignancies [59].

Graft versus host disease (GVHD) is one of the major early and late morbidity and mortality causes. It has been proven that donor source has an impact on GVHD rates. Although the HLA disparities were higher in cord blood transplantations, GVHD was found to be lower than bone marrow [60–62]. Eurocord and EBMT revealed that HLA mismatch increased the acute GVHD risk in cord blood transplantation [63]. Patient age [51], CMV status [63], nonmyeloablative conditioning, and absence of ATG were also factors thought to be related with acute GVHD. Acute GVHD was reported to be higher in double-unit cord transplants than the single-unit transplants [60]. In a study with 1072 patients, chronic GVHD in posttransplant 2 years was 28%. In multivariate analysis, risk factors were identified as myeloablative conditioning regimen, mycophenolate mofetil in GVHD prophylaxis, increased HLA mismatch, higher body weight, and previous acute GVHD [64]. Newell et al. [65] found higher chronic GVHD rates, which were analyzed according to NIH 2005 criteria and had a predominance of acute GVHD features.

Comparative trials of umbilical cord blood with different stem cell sources have been reported. Neutrophil and platelet recovery have been delayed in cord blood transplantations, and chronic GVHD rates have been observed less. Laughlin et al. [66] included patients who had received either an HLA-matched marrow transplant- a marrow transplant with a single HLA mismatch from an unrelated donor or who had received a cord blood transplant with one or two HLA mismatches in their study. Overall mortality was found to be lower in matched related BM recipients. The rate of leukemia recurrence was found to be similar, but 3 years survival for cord blood recipients was 26%, which was lower than matched BM recipients' survival. In a recent trial, donor types have been investigated in AML patients; survival rates were similar between matched related, matched unrelated, mismatched unrelated, and cord blood transplant. Age and type of conditioning regimens were the major determinants of survival [67].

As a consequence of inadequate engraftment with single-unit cord blood transplantation in adult hematological malignancy patients, double-unit cord transplantation was introduced in the beginning of 2000s. Sustained engraftment could be achieved more than 90% of patients and one of the double-units dominate [68,69]. Barker et al. [70] observed the impact of CD3+ cell dose on engraftment, but not the CD34+ cell dose or HLA match in double cord unit transplantations.

Avery et al. [68] found an association between higher numbers of CD34+ and TNC cell dose of the dominant unit and sustained engraftment. In the same trial, unit-unit HLA match and unit-recipient HLA match were not associated with sustained engraftment. Mixed chimerism can be displayed in follow-up, especially if the HLA match of the both units is close [71]. The HOVON group showed that the unit predominance was observed by posttransplant day 11, and the role of CD4+ lymphocyte-mediated alloreactivity was suggested [72]. In another study, the cord blood bank reported pre cryopreservation and postthaw viable CD34+ cell doses were the important parameters for the engraftment [73].

Macmillan et al. [60] reported double cord transplantation as one of the risk factors for acute GVHD. Ponce et al. [74] demonstrated the acute grades II-IV rates as 53% and predominantly the gut as affected organ. Chronic GVHD rates have been reported around 30% in double cord blood transplantation trials [75,76].

Eurocord and EBMT compared single-unit transplantation with different myeloablative conditioning regimens and double-unit transplantation. Conditioning regimens were either the widely accepted Minnesota protocol, which consisted of TBI/cyclophosphamide/fludarabine or thiotepa/busulphan/fludarabine (TBF). In this study, 2 years LFS was similar between double-unit cord and single-unit cord if the new TBF protocol was chosen [75,77]. In a prospective multicenter trial, which included 56 acute leukemia and myelodysplasia patients transplanted with double-unit cord, 3 years disease-free survival was 50% and TRM was 39% [76].

Comparative studies of different stem cell sources in the era of double-unit cord have been continued to be reported. In comparison with filgrastim mobilized peripheral blood, delay in immune reconstitution of T cells in cord blood transplantation resulted in increased infection

risks. The double-unit cord blood has been compared with unrelated donor grafts; although 3 years survival analysis were similar, double cord blood was associated with less chronic GVHD but more nonrelapse mortality [78]. Brunstein et al. [79] have found comparable 5-year leukemia-free survival after HLA-matched related, unrelated, and double-unit cord blood transplantation.

4. Hematopoietic progenitor cell and umbilical cord blood cryopreservation

Collected hematopoietic stem cells have been cryopreserved by using a cryoprotectant, dimethyl sulfoxide (DMSO), and frozen in liquid nitrogen vapor until reinfusion. DMSO penetrates to cells and binds to water molecules in order to prevent dehydration of the cells [80]. During the cryopreservation process, DMSO dilution, freezing period, storage in vapor phase, or liquid nitrogen are the important factors for optimum results. DMSO and cell suspension should be cooled down to 0°C–4°C, and after the addition of DMSO, the product should be placed in a controlled freezer subsequently. The optimum concentration of DMSO has also been analyzed in different studies because it can be toxic for stem cell viability and also may cause side effects during infusion. Although majority of transplant centers still prefer to use 10% DMSO, lower percentage of DMSO or washing the product before infusion to decrease toxicity has also been used [81]. Reducing DMSO concentration into 7.5% has been revealed as feasible [82]. Up to 10 years cryopreservation with 5% DMSO has also been found not to have a negative impact on cell viability [83]. DMSO concentration has been calculated as ml/kg body weight or ml/min, and in EBMT results from 65 centers, it has been revealed that calculation as milliliters per minute should be the preferred way to reduce side effects [84]. DMSO toxicity can result in nausea, vomiting, fever, or more severe reactions like hepatic dysfunction, cardiac arrhythmia, and neurotoxicity [85,86].

In the freezing period, cells have been mostly frozen using controlled rate freezers. Too fast cooling can result in intracellular crystallization, and too slow cooling can induce extracellular ice formation. Sputtek et al. [87] reported that the cooling rate range can vary from 1 to 5 K/min. Also, the recovery of white blood cell (WBC) recovery was found to be superior in slow rate freezing to fast rate freezing [88]. After the introduction of stem cell storage in liquid nitrogen, risks for microbial contamination of the products concluded with the usage of vapor phase for storage. However, the comparison of the two phase was found to be similar for either WBC recovery or WBC viability in comparative studies [88,89].

The major disadvantage of the umbilical cord blood processing is the potential risk for loss of progenitor cells in the collected product. The techniques that have been used for red cell separation like simple centrifugation lysis with ammonium chloride, filtration through density gradients, or collection from bags to vessels were found to have detrimental effects during cryopreservation [90–93]. Thus, Rubinstein et al. [94] initially proved that forming 20 ml cord blood units with uniform volume can be achieved by using rouleaux formation induced by hydroxyethyl starch and centrifugation. Semiautomated top–bottom systems and lately

automatic devices like AXP-SEPAX have been developed [95]. Automatic systems could achieve similar cell recovery with less technical influence [96].

After the addition of 10% dimethyl sulfoxide, cord blood samples can be cooled from 4°C to –80°C mostly by controlled rate freezers [97]. It has been recently shown that cord bloods can be transferred into liquid nitrogen vapor phase directly or after storage at –80°C for 18 hours [98]. It has been demonstrated by Broxmeyer et al. that the long-term storage does not have a negative influence on in vitro function of umbilical cord blood progenitor cells. Also, the duration of cryopreservation was found to have no impact on clinical outcome like neutrophil or platelet recovery after cord blood transplantation [99].

5. Conclusion

Hematopoietic stem cell source choice is an important issue to be concerned during stem cell transplantation. Diagnosis and pretransplantation status of hematological diseases and type of conditioning regimens are the major factors in making decision for one type of stem cell source.

Processing before the storage of collected stem cells can show differences according to the source of stem cells. In particular, cord blood processing needs more attention due to the risk of hematopoietic stem cell loss.

Author details

Sinem Civriz Bozdag* and Osman İlhan*

*Address all correspondence to: osmanilhan@medicine.ankara.edu.tr

Stem Cell Transplantation Unit, Department of Hematology, School of Medicine, Ankara University, Ankara, Turkey

References

- [1] Faucher C, le Corroller AG, Blaise D, Novakovitch G, Manonni P, Moatti JP, Maraninchi D. Comparison of G-CSF-primed peripheral blood progenitor cells and bone marrow auto transplantation: clinical assessment and cost-effectiveness. *Bone Marrow Transplant*. 1994 Dec;14(6):895–901.
- [2] Faucher C, Le Corroller AG, Chabannon C, Viens P, Stoppa AM, Bouabdallah R, Camerlino J, Vey N, Gravis G, Gastaut JA, Novakovitch G, Mannoni P, Bardou VJ, Moatti JP, Maraninchi D, Blaise D. Autologous transplantation of blood stem cells mobilized

- with filgrastim alone in 93 patients with malignancies: the number of CD34+ cells re-infused is the only factor predicting both granulocyte and platelet recovery. *J Hematother.* 1996 Dec;5(6):663–70.
- [3] Bensinger WI, Weaver CH, Appelbaum FR, Rowley S, Demirer T, Sanders J, Storb R, Buckner CD. Transplantation of allogeneic peripheral blood stem cells mobilized by recombinant human granulocyte colony-stimulating factor. *Blood.* 1995 Mar 15;85(6):1655–8.
 - [4] Duncan N, Hewetson M, Powles R, Raje N, Mehta J. An economic evaluation of peripheral blood stem cell transplantation as an alternative to autologous bone marrow transplantation in multiple myeloma. *Bone Marrow Transplant.* 1996 Dec;18(6):1175–8.
 - [5] Bensinger WI, Clift R, Martin P, Appelbaum FR, Demirer T, Gooley T, Lilleby K, Rowley S, Sanders J, Storb R, Buckner CD. Allogeneic peripheral blood stem cell transplantation in patients with advanced hematologic malignancies: a retrospective comparison with marrow transplantation. *Blood.* 1996 Oct 1;88(7):2794–800.
 - [6] Ustün C, Arslan O, Beksaç M, Koç H, Gürman G, Özçelik T, Yilmaz B, İlhan O, Akan H, Özcan M, Demirer T, Uysal A, Konuk N, Arat M, Dilek I, Celebi H, Coskun HS. A retrospective comparison of allogeneic peripheral blood stem cell and bone marrow transplantation results from a single center: a focus on the incidence of graft-vs.-host disease and relapse. *Biol Blood Marrow Transplant.* 1999;5(1):28–35.
 - [7] Mifflin G, Russell NH, Hutchinson RM, Morgan G, Potter M, Pagliuca A, Marsh J, Bell A, Milligan D, Lumley M, Cook G, Franklin. Allogeneic peripheral blood stem cell transplantation for haematological malignancies—an analysis of kinetics of engraftment and GVHD risk. *Bone Marrow Transplant.* 1997 Jan;19(1):9–13.
 - [8] Schmitz N, Bacigalupo A, Hasenclever D, Nagler A, Gluckman E, Clark P, Bourquelot P, Greinix H, Frickhofen N, Ringdén O, Zander A, Apperley JF, Gorin C, Borkett K, Schwab G, Goebel M, Russell NH, Gratwohl A. Allogeneic bone marrow transplantation vs filgrastim-mobilised peripheral blood progenitor cell transplantation in patients with early leukaemia: first results of a randomised multicentre trial of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 1998 May;21(10):995–1003.
 - [9] Mielcarek M, Storer B, Martin PJ, Forman SJ, Negrin RS, Flowers ME, Inamoto Y, Chauncey TR, Storb R, Appelbaum FR, Bensinger WI. Long-term outcomes after transplantation of HLA-identical related G-CSF-mobilized peripheral blood mononuclear cells versus bone marrow. *Blood.* 2012 Mar 15;119(11):2675–8.
 - [10] Holtick U, Albrecht M, Chemnitz JM, Theurich S, Skoetz N, Scheid C, von Bergwelt-Baildon M. Bone marrow versus peripheral blood allogeneic haematopoietic stem cell transplantation for haematological malignancies in adults. *Cochrane Database Syst Rev.* 2014 Apr 20;4:CD010189.

- [11] Urbano-Ispizua A, Rozman C, Pimentel P, Solano C, de la Rubia J, Brunet S, Pérez-Oteyza J, Ferrá C, Zuazu J, Caballero D, Bargay J, Carvalhais A, Díez JL, Espigado I, Alegre A, Rovira M, Campilho F, Odriozola J, Sanz MA, Sierra J, García-Conde J, Montserrat E; Spanish Group for Allogeneic Peripheral Blood Transplantation (Grupo Español de Trasplante Hemopoyético) and Instituto Português de Oncologia-Porto. Risk factors for acute graft-versus-host disease in patients undergoing transplantation with CD34+ selected blood cells from HLA-identical siblings. *Blood*. 2002 Jul 15;100(2):724–7.
- [12] Zaucha JM, Gooley T, Bensinger WI, Heimfeld S, Chauncey TR, Zaucha R, Martin PJ, Flowers ME, Storek J, Georges G, Storb R, Torok-Storb B. CD34 cell dose in granulocyte colony-stimulating factor-mobilized peripheral blood mononuclear cell grafts affects engraftment kinetics and development of extensive chronic graft-versus-host disease after human leukocyte antigen-identical sibling transplantation. *Blood*. 2001 Dec 1;98(12):3221–7.
- [13] Urbano-Ispizua A. Chronic graft versus host disease after allogeneic peripheral blood transplantation. *Haematologica*. 2003 Mar;88(3):245–6.
- [14] Lee SJ. Have we made progress in the management of chronic graft-vs-host disease? *Best Pract Res Clin Haematol*. 2010 Dec;23(4):529–35.
- [15] Boyiadzis M, Arora M, Klein J, Hassebroek A, Hemmer M, Urbano-Ispizua A, Antin JH, Bolwell B, Cahn JY, Cairo MS, Cutler C, Flowers M, Gale R, Herzig R, Isola L, Jacobsohn D, Jagasia M, Klumpp T, Lee SJ, Petersdorf E, Santarone S, Spellman S, Schouten HC, Verdonck L, Wingard J, Weisdorf D, Horowitz M, Pavletic S. Impact of chronic graft-versus-host disease on late relapse and survival on 7489 patients after myeloablative allogeneic hematopoietic cell transplantation for leukemia. *Clin Cancer Res*. 2014 Oct 27.
- [16] Cheuk DK. Optimal stem cell source for allogeneic stem cell transplantation for hematological malignancies. *World J Transplant*. 2013 Dec 24;3(4):99–112.
- [17] Pidala J, Anasetti C, Kharfan-Dabaja MA, Cutler C, Sheldon A, Djulbegovic B. Decision analysis of peripheral blood versus bone marrow hematopoietic stem cells for allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2009 Nov;15(11):1415–21.
- [18] Stem Cell Trialists' Collaborative Group. Allogeneic peripheral blood stem-cell compared with bone marrow transplantation in the management of hematologic malignancies: an individual patient data meta-analysis of nine randomized trials. *J Clin Oncol*. 2005; 23: 5074–87.
- [19] Couban S, Simpson DR, Barnett MJ, Bredeson C, Hubesch L, Howson-Jan K, Shore TB, Walker IR, Browett P, Messner HA, Panzarella T, Lipton JH; Canadian Bone Marrow Transplant Group. A randomized multicenter comparison of bone marrow and

peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. *Blood*. 2002 Sep 1;100(5):1525–31.

- [20] Oehler VG, Radich JP, Storer B, Blume KG, Chauncey T, Clift R, Snyder DS, Forman SJ, Flowers ME, Martin P, Guthrie KA, Negrin RS, Appelbaum FR, Bensinger W. Randomized trial of allogeneic related bone marrow transplantation versus peripheral blood stem cell transplantation for chronic myeloid leukemia. *Biol Blood Marrow Transplant*. 2005 Feb;11(2):85–92.
- [21] Dufour C, Pillon M, Passweg J, Socié G, Bacigalupo A, Franceschetto G, Carraro E, Oneto R, Risitano AM, Peffault de Latour R, Tichelli A, Rovo A, Peters C, Hoehs-mann B, Samarasinghe S, Kulasekararaj AG, Schrezenmeier H, Aljurf M, Marsh J. Outcome of aplastic anemia in adolescence: a survey of the Severe Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation. *Haematologica*. 2014 Oct;99(10):1574–81.
- [22] Bacigalupo A, Socié G, Schrezenmeier H, Tichelli A, Locasciulli A, Fuehrer M, Risitano AM, Dufour C, Passweg JR, Oneto R, Aljurf M, Flynn C, Mialou V, Hamladji RM, Marsh JC; Aplastic Anemia Working Party of the European Group for Blood and Marrow Transplantation (WPSAA-EBMT). Bone marrow versus peripheral blood as the stem cell source for sibling transplants in acquired aplastic anemia: survival advantage for bone marrow in all age groups. *Haematologica*. 2012 Aug;97(8):1142–8.
- [23] Chu R, Brazauskas R, Kan F, Bashey A, Bredeson C, Camitta B, Chiang KY, Frangoul H, Gale RP, Gee A, George B, Goldman FD, Gross TG, Gupta V, Hale GA, Isola L, Ispizua AU, Lazarus H, Marsh J, Russell J, Sabloff M, Waller EK, Eapen M. Comparison of outcomes after transplantation of G-CSF-stimulated bone marrow grafts versus bone marrow or peripheral blood grafts from HLA-matched sibling donors for patients with severe aplastic anemia. *Biol Blood Marrow Transplant*. 2011 Jul;17(7):1018–24.
- [24] Friedrichs B, Tichelli A, Bacigalupo A, Russell NH, Ruutu T, Shapira MY, Beksac M, Hasenclever D, Socié G, Schmitz N. Long-term outcome and late effects in patients transplanted with mobilised blood or bone marrow: a randomised trial. *Lancet Oncol*. 2010 Apr;11(4):331–8.
- [25] Eapen M, Logan BR, Confer DL, Haagenson M, Wagner JE, Weisdorf DJ, Wingard JR, Rowley SD, Stroncek D, Gee AP, Horowitz MM, Anasetti C. Peripheral blood grafts from unrelated donors are associated with increased acute and chronic graft-versus-host disease without improved survival. *Biol Blood Marrow Transplant*. 2007 Dec;13(12):1461–8.
- [26] Anasetti C, Logan BR, Lee SJ, Waller EK, Weisdorf DJ, Wingard JR, Cutler CS, Westervelt P, Woolfrey A, Couban S, Ehninger G, Johnston L, Maziarz RT, Pulsipher MA, Porter DL, Mineishi S, McCarty JM, Khan SP, Anderlini P, Bensinger WI, Leitman SF, Rowley SD, Bredeson C, Carter SL, Horowitz MM, Confer DL; Blood and Marrow

Transplant Clinical Trials Network. Peripheral-blood stem cells versus bone marrow from unrelated donors. *N Engl J Med*. 2012 Oct 18;367(16):1487–96.

- [27] Eapen M, Logan BR, Appelbaum FR, Antin JH, Anasetti C, Couriel DR, Chen J, Maziarz RT, McCarthy PL, Nakamura R, Ratanatharathorn V, Vij R, Champlin RE. Long-term survival after transplantation of unrelated donor peripheral blood or bone marrow hematopoietic cells for hematologic malignancy. *Biol Blood Marrow Transplant*. 2015 Jan;21(1):55–9.
- [28] Shin SH, Kim JH, Jeon YW, Yoon JH, Yahng SA, Lee SE, Cho BS, Eom KS, Kim YJ, Lee S, Min CK, Cho SG, Kim DW, Lee JW, Min WS, Park CW, Kim HJ. Similar outcomes of peripheral blood stem cells vs. bone marrow for human leukocyte antigen-matched unrelated donor transplantation in adult patients with acute myeloid leukemia using risk-adapted graft-versus-host disease prophylaxis. *Eur J Haematol*. 2014 Jul;93(1):19–28.
- [29] Bacigalupo A, Socié G, Hamladji RM, Aljurf M, Maschan A, Kyrz-Krzemien S, Cybicka A, Sengelov H, Unal A, Beelen D, Locasciulli A, Dufour C, Passweg JR, Oneto R, Signori A, Marsh JC. Current outcome of HLA identical sibling vs. unrelated donor transplants in severe aplastic anemia: an EBMT analysis. *Haematologica*. 2015 Jan 23.
- [30] Nagler A, Labopin M, Shimoni A, Mufti GJ, Cornelissen JJ, Blaise D, Janssen JJ, Milpied N, Vindelov L, Petersen E, Gribben J, Bacigalupo A, Malm C, Niederwieser D, Socié GJ, Arnold R, Brown P, Goker H, Rocha V, Mohty M; ALWP-EBMT. Mobilized peripheral blood stem cells compared with bone marrow from HLA-identical siblings for reduced-intensity conditioning transplantation in acute myeloid leukemia in complete remission: a retrospective analysis from the Acute Leukemia Working Party of EBMT. *Eur J Haematol*. 2012 Sep;89(3):206–13.
- [31] Eapen M, Logan BR, Horowitz MM, Zhong X, Perales MA, Lee SJ, Rocha V, Soiffer RJ, Champlin RE. Bone marrow or peripheral blood for reduced-intensity conditioning unrelated donor transplantation. *J Clin Oncol*. 2015 Feb 1;33(4):364–9.
- [32] Demirer T, Ilhan O, Ayli M, Arat M, Dagli M, Ozcan M, Haznedar R, Genc Y, Fen T, Ayyildiz E, Dincer S, Arslan O, Gurman G, Konuk N, Dalva K, Uysal A, Koc H, Ozet G, Akan H. Monitoring of peripheral blood CD34+ cell counts on the first day of apheresis is highly predictive for efficient CD34+ cell yield. *Ther Apher*. 2002 Oct;6(5):384–9.
- [33] Bolan CD, Hartzman RJ, Perry EH, Trainor L, Miller J, Miller R, Hanley L, Chitphakdithai P, King RJ. Donation activities and product integrity in unrelated donor allogeneic hematopoietic transplantation: experience of the National Marrow Donor Program. *Biol Blood Marrow Transplant*. 2008 Sep;14(9 Suppl):23–8.

- [34] Arat M, Arslan O, Ayyildiz E, Topcuoglu P, Dalva K, Ilhan O. Peripheral blood stem cell apheresis for allogeneic transplants: Ibni Sina experience. *Transfus Apheresis Sci.* 2004 Jun;30(3):189–91.
- [35] Switzer GE, Bruce JG, Harrington D, Haagenson M, Drexler R, Foley A, Confer D, Bishop M, Anderlini P, Rowley S, Leitman SF, Anasetti C, Wingard JR. Health-related quality of life of bone marrow versus peripheral blood stem cell donors: a prespecified subgroup analysis from a phase III RCT-BMTCTN protocol 0201. *Biol Blood Marrow Transplant.* 2014 Jan;20(1):118–27.
- [36] Halter J1, Kodera Y, Ispizua AU, Greinix HT, Schmitz N, Favre G, Baldomero H, Niederwieser D, Apperley JF, Gratwohl A. Severe events in donors after allogeneic hematopoietic stem cell donation. *Haematologica.* 2009 Jan;94(1):94–101.
- [37] Miller JP, Perry EH, Price TH, Bolan CD Jr, Karanes C, Boyd TM, Chitphakdithai P, King RJ. Recovery and safety profiles of marrow and PBSC donors: experience of the National Marrow Donor Program. *Biol Blood Marrow Transplant.* 2008 Sep;14(9 Suppl):29–36.
- [38] Pulsipher MA, Chitphakdithai P, Logan BR, Navarro WH, Levine JE, Miller JP, Shaw BE, O'Donnell PV, Majhail NS, Confer DL. Lower risk for serious adverse events and no increased risk for cancer after PBSC vs BM donation. *Blood.* 2014 Jun 5;123(23):3655–63.
- [39] Auerbach AD, Liu Q, Ghosh R, Pollack MS, Douglas GW, Broxmeyer HE. Prenatal identification of potential donors for umbilical cord blood transplantation for Fanconi anemia. *Transfusion.* 1990;30(8):682–687.
- [40] Gragert L, Eapen M, Williams E, Freeman J, Spellman S, Baitty R, Hartzman R, Rizzo JD, Horowitz M, Confer D, Maiers M. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry. *N Engl J Med.* 2014 Jul 24;371(4):339–48.
- [41] Danby R, Rocha V. Improving engraftment and immune reconstitution in umbilical cord blood transplantation. *Front Immunol.* 2014 Feb 24;5:68.
- [42] Eapen M, Klein JP, Sanz GF, Spellman S, Ruggeri A, Anasetti C, Brown M, Champlin RE, Garcia-Lopez J, Hattersely G, Koegler G, Laughlin MJ, Michel G, Nabhan SK, Smith FO, Horowitz MM, Gluckman E, Rocha V; Eurocord-European Group for Blood and Marrow Transplantation; Netcord; Center for International Blood and Marrow Transplant Research. Effect of donor-recipient HLA matching at HLA A, B, C, and DRB1 on outcomes after umbilical-cord blood transplantation for leukaemia and myelodysplastic syndrome: a retrospective analysis. *Lancet Oncol.* 2011 Dec;12(13):1214–21.
- [43] Eapen M, Klein JP, Ruggeri A, Spellman S, Lee SJ, Anasetti C, Arcese W, Barker JN, Baxter-Lowe LA, Brown M, Fernandez-Vina MA, Freeman J, He W, Iori AP, Horowitz MM, Locatelli F, Marino S, Maiers M, Michel G, Sanz GF, Gluckman E, Rocha V; Center for International Blood and Marrow Transplant Research, Netcord, Eurocord,

- and the European Group for Blood and Marrow Transplantation. Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy. *Blood*. 2014 Jan 2;123(1):133–40.
- [44] Ballen KK, Gluckman E, Broxmeyer HE. Umbilical cord blood transplantation: the first 25 years and beyond. *Blood*. 2013 Jul 25;122(4):491–8.
- [45] Barker JN, Scaradavou A, Stevens CE. Combined effect of total nucleated cell dose and HLA match on transplantation outcome in 1061 cord blood recipients with hematologic malignancies. *Blood*. 2010 Mar 4;115(9):1843–9.
- [46] van Heeckeren WJ, Fanning LR, Meyerson HJ, Fu P, Lazarus HM, Cooper BW, Tse WW, Kindwall-Keller TL, Jaroscak J, Finney MR, Fox RM, Solchaga L, Forster M, Creger RJ, Laughlin MJ. Influence of human leucocyte antigen disparity and graft lymphocytes on allogeneic engraftment and survival after umbilical cord blood transplant in adults. *Br J Haematol*. 2007 Nov;139(3):464–74.
- [47] Cunha R, Loiseau P, Ruggeri A, Sanz G, Michel G, Paolaiori A, Socié G, Arcese W, Picardi A, Dias de Heredia C, Rio B, Locatelli F, O'Brien TA, Yakoub-Agha I, Angel Diaz M, Milpied N, Bittencourt H, Pedro Souza M, Aljurf M, Charron D, Boudjedir K, Labopin M, Gluckman E, Rocha V. Impact of HLA mismatch direction on outcomes after umbilical cord blood transplantation for hematological malignant disorders: a retrospective Eurocord-EBMT analysis. *Bone Marrow Transplant*. 2014 Jan; 49(1):24–9.
- [48] Kekre N, Antin JH. Hematopoietic stem cell transplantation donor sources in the 21st century: choosing the ideal donor when a perfect match does not exist. *Blood*. 2014 Jul 17;124(3):334–43.
- [49] Migliaccio AR, Adamson JW, Stevens CE, Dobrila NL, Carrier CM, Rubinstein P. Cell dose and speed of engraftment in placental/umbilical cord blood transplantation: graft progenitor cell content is a better predictor than nucleated cell quantity. *Blood*. 2000 Oct 15;96(8):2717–22.
- [50] Ruggeri A, Labopin M, Sormani MP, Sanz G, Sanz J, Volt F, Michel G, Locatelli F, Diaz De Heredia C, O'Brien T, Arcese W, Iori AP, Querol S, Kogler G, Lecchi L, Pouthier F, Garnier F, Navarrete C, Baudoux E, Fernandes J, Kenzey C, Eapen M, Gluckman E, Rocha V, Saccardi R; Eurocord; Cord Blood Committee EBMT; Netcord. Engraftment kinetics and graft failure after single umbilical cord blood transplantation using a myeloablative conditioning regimen. *Haematologica*. 2014 Sep;99(9):1509–15.
- [51] Rubinstein P, Carrier C, Scaradavou A, Kurtzberg J, Adamson J, Migliaccio AR, Berkowitz RL, Cabbad M, Dobrila NL, Taylor PE, Rosenfield RE, Stevens CE. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. *N Engl J Med*. 1998 Nov 26;339(22):1565–77.
- [52] Cohen YC, Scaradavou A, Stevens CE, Rubinstein P, Gluckman E, Rocha V, Horowitz MM, Eapen M, Nagler A, Shpall EJ, Laughlin MJ, Daniely Y, Pacheco D, Barish-

- ev R, Olmer L, Freedman LS. Factors affecting mortality following myeloablative cord blood transplantation in adults: a pooled analysis of three international registries. *Bone Marrow Transplant*. 2011 Jan;46(1):70–6.
- [53] Ooi J, Takahashi S, Tomonari A, Tsukada N, Konuma T, Kato S, Kasahara S, Sato A, Monma F, Nagamura F, Iseki T, Tojo A, Asano S. Unrelated cord blood transplantation after myeloablative conditioning in adults with acutemyelogenous leukemia. *Biol Blood Marrow Transplant*. 2008 Dec;14(12):1341–7.
- [54] Tucunduva L, Ruggeri A, Sanz G, Furst S, Socié G, Michallet M, Arcese W, Milpied N, Yakoub-Agha I, Linkesch W, Cornelissen J, Mannone L, Iori AP, Ribera JM, Sanz J, Montesinos P, Purtill D, Labopin M, Gluckman E, Mohty M, Rocha V. Risk factors for outcomes after unrelated cord blood transplantation for adults with acute lymphoblastic leukemia: a report on behalf of Eurocord and the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2014 Jul;49(7):887–94.
- [55] Brunstein C, Barker JN, Weisdorf D, DeFor TE, Miller JS, Blazar BR, McGlave PB, Wagner JE. Umbilical cord blood transplantation after nonmyeloablative conditioning: impact on transplant outcomes in 110 adults with hematological disease. *Blood*. 2007;110(8):3064–3070.
- [56] Oran B, Wagner JE, DeFor TE, Weisdorf DJ, Brunstein CG. Effect of conditioning regimen intensity on acute myeloid leukemia outcomes after umbilical cord blood transplantation. *Biol Blood Marrow Transplant*. 2011 Sep;17(9):1327–34.
- [57] Uchida N, Wake A, Takagi S, Yamamoto H, Kato D, Matsuhashi Y, Matsumura T, Seo S, Matsuno N, Masuoka K, Kusumi E, Yuji K, Miyakoshi S, Matsuzaki M, Yoneyama A, Taniguchi S. Umbilical cord blood transplantation after reduced-intensity conditioning for elderly patients with hematologic diseases. *Biol Blood Marrow Transplant*. 2008 May;14(5):583–90.
- [58] Barker JN, Weisdorf DJ, DeFor TE, Blazar BR, Miller JS, Wagner JE. Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced intensity conditioning. *Blood*. 2003;102(5): 1915–1919.
- [59] Mori T, Tanaka M, Kobayashi T, Ohashi K, Fujisawa S, Yokota A, Fujita H, Nakaseko C, Sakura T, Nannya Y, Takahashi S, Kanamori H, Kanda Y, Sakamaki H, Okamoto S; Kanto Study Group for Cell Therapy. Prospective multicenter study of single-unit cord blood transplantation with myeloablative conditioning for adult patients with high-risk hematologic malignancies. *Biol Blood Marrow Transplant*. 2013 Mar;19(3): 486–91.
- [60] MacMillan ML, Weisdorf DJ, Brunstein CG, Cao Q, DeFor TE, Verneris MR, Blazar BR, Wagner JE. Acute graft-versus-host disease after unrelated donor umbilical cord blood transplantation: analysis of risk factors. *Blood*. 2009 Mar 12;113(11):2410–5.
- [61] Rocha V, Labopin M, Sanz G, Arcese W, Schwerdtfeger R, Bosi A, Jacobsen N, Ruutu T, de Lima M, Finke J, Frassoni F, Gluckman E; Acute Leukemia Working Party of

- European Blood and Marrow Transplant Group; Eurocord-Netcord Registry. Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. *N Engl J Med* 2004;351:2276–2285.
- [62] Grewal SS, Barker JN, Davies SM, Wagner JE. Unrelated donor hematopoietic cell transplantation: marrow or umbilical cord blood? *Blood* 2003;101:4233–4244.
- [63] Gluckman E, Rocha V, Arcese W, Michel G, Sanz G, Chan KW, Takahashi TA, Ortega J, Filipovich A, Locatelli F, Asano S, Fagioli F, Vowels M, Sirvent A, Laporte JP, Tiedemann K, Amadori S, Abecassis M, Bordigoni P, Diez B, Shaw PJ, Vora A, Caniglia M, Garnier F, Ionescu I, Garcia J, Koegler G, Rebutta P, Chevret S; Eurocord Group. Factors associated with outcomes of unrelated cord blood transplant: guidelines for donor choice. *Exp Hematol*. 2004;32(4):397–407.
- [64] Narimatsu H, Miyakoshi S, Yamaguchi T, Kami M, Matsumura T, Yuji K, Murashige N, Kusumi E, Kodama Y, Komatsu T, Sakamaki H, Kouzai Y, Okada M, Osugi Y, Kobayashi R, Inoue M, Takahashi S, Kai S, Kato K, Inoue-Nagamura T, Taniguchi S, Kato S; Japan Cord Blood Bank Network. Chronic graft-versus-host disease following umbilical cord blood transplantation: retrospective survey involving 1072 patients in Japan. *Blood*. 2008 Sep 15;112(6):2579–82.
- [65] Newell LF, Flowers ME, Gooley TA, Milano F, Carpenter PA, Martin PJ, Delaney C. Characteristics of chronic GVHD after cord blood transplantation. *Bone Marrow Transplant*. 2013 Oct;48(10):1285–90.
- [66] Laughlin MJ, Eapen M, Rubinstein P, Wagner JE, Zhang MJ, Champlin RE, Stevens C, Barker JN, Gale RP, Lazarus HM, Marks DI, van Rood JJ, Scaradavou A, Horowitz MM. Outcomes after transplantation of cord blood or bone marrow from unrelated donors in adults with leukemia. *N Engl J Med*. 2004 Nov 25;351(22):2265–75.
- [67] Warlick ED, Peffault de Latour R, Shanley R, Robin M, Bejanyan N, Xhaard A, Brunstein C, Sicre de Fontbrune F, Ustun C, Weisdorf DJ, Socie G. Allogeneic hematopoietic cell transplantation outcomes in acute myeloid leukemia: similar outcomes regardless of donor type. *Biol Blood Marrow Transplant*. 2015 Feb;21(2):357–63.
- [68] Avery S, Shi W, Lubin M, Gonzales AM, Heller G, Castro-Malaspina H, Giralt S, Kernan NA, Scaradavou A, Barker JN. Influence of infused cell dose and HLA-match on engraftment after double-unit cord blood allografts. *Blood*. 2011 Mar 24;117(12):3277–85.
- [69] Rocha V, Crotta A, Ruggeri A, Purtill D, Boudjedir K, Herr AL, Ionescu I, Gluckman E; Eurocord Registry. Double cord blood transplantation: extending the use of unrelated umbilical cord blood cells for patients with hematological diseases. *Best Pract Res Clin Haematol*. 2010 Jun;23(2):223–9.
- [70] Barker JN, Weisdorf DJ, DeFor TE, Blazar BR, McGlave PB, Miller JS, Verfaillie CM, Wagner JE. Transplantation of two partially HLA-matched umbilical cord blood

- units to enhance engraftment in adults with hematologic malignancy. *Blood* 2005;105(3):1343–1347.
- [71] Brunstein CG, Gutman JA, Weisdorf DJ, Woolfrey AE, Defor TE, Gooley TA, Verneiris MR, Appelbaum FR, Wagner JE, Delaney C. Allogeneic hematopoietic cell transplantation for hematologic malignancy: relative risks and benefits of double umbilical cord blood. *Blood*. 2010;116(22):4693–4699.
- [72] Somers JA, Braakman E, van der Holt B, Petersen EJ, Marijt EW, Huisman C, Sintnicolaas K, Oudshoorn M, Groenendijk-Sijne ME, Brand A, Cornelissen JJ. Rapid induction of single donor chimerism after double umbilical cord blood transplantation preceded by reduced intensity conditioning: results of the HOVON 106 phase II study. *Haematologica*. 2014 Nov;99(11):1753–61.
- [73] Purtill D, Smith K, Devlin S, Meagher R, Tonon J, Lubin M, Ponce DM, Giralt S, Kernan NA, Scaradavou A, Stevens CE, Barker JN. Dominant unit CD34+ cell dose predicts engraftment after double-unit cord blood transplantation and is influenced by bank practice. *Biol Blood Marrow Transplant*. 2013 Jun;19(6):904–11.
- [74] Ponce DM, Gonzales A, Lubin M, Castro-Malaspina H, Giralt S, Goldberg JD, Hanash AM, Jakubowski A, Jenq R, Papadopoulos EB, Perales MA, van den Brink MR, Young JW, Boulad F, O'Reilly RJ, Prockop S, Small TN, Scaradavou A, Kernan NA, Stevens CE, Barker JN. Graft-versus-host disease after double-unit cord blood transplantation has unique features and an association with engrafting unit-to-recipient HLA match. *Blood*. 2014 Nov 6;124(19):2905–12.
- [75] Ruggeri A, Sanz G, Bittencourt H, Sanz J, Rambaldi A, Volt F, Yakoub-Agha I, Ribera JM, Mannone L, Sierra J, Mohty M, Solano C, Nabhan S, Arcese W, Gluckman E, Labopin M, Rocha V; Eurocord and Acute Leukemia Working Party of European Blood and Marrow Transplant Group. Comparison of outcomes after single or double cord blood transplantation in adults with acute leukemia using different types of myeloablative conditioning regimen, a retrospective study on behalf of Eurocord and the Acute Leukemia Working Party of EBMT. *Leukemia*. 2014 Apr;28(4):779–86.
- [76] Barker JN, Fei M, Karanes C, Horwitz M, Devine S, Kindwall-Keller TL, Holter J, Adams A, Logan B, Navarro WH, Riches M; RCI BMT 05-DCB Protocol Team. Results of a prospective multicentre myeloablative double-unit cord blood transplantation trial in adult patients with acute leukaemia and myelodysplasia. *Br J Haematol*. 2015 Feb;168(3):405–12.
- [77] Abedin S, Peres E, Levine JE, Choi S, Yanik G, Couriel DR. Double umbilical cord blood transplantation after novel myeloablative conditioning using a regimen of fludarabine, busulfan, and total lymphoid irradiation. *Biol Blood Marrow Transplant*. 2014 Dec;20(12):2062–6.
- [78] Chen YB, Aldridge J, Kim HT, Ballen KK, Cutler C, Kao G, Liney D, Bourdeau G, Alyea EP, Armand P, Koreth J, Ritz J, Spitzer TR, Soiffer RJ, Antin JH, Ho VT. Reduced intensity conditioning stem cell transplantation: comparison of double umbili-

cal cord blood and unrelated donor grafts. *Biol Blood Marrow Transplant*. 2012;18(5):805–12.

- [79] Brunstein CG, Fuchs EJ, Carter SL, Karanes C, Costa LJ, Wu J, Devine SM, Wingard JR, Aljitawi OS, Cutler CS, Jagasia MH, Ballen KK, Eapen M, O'Donnell PV; Blood and Marrow Transplant Clinical Trials Network. Alternative donor transplantation after reduced intensity conditioning: results of parallel phase 2 trials using partially HLA-mismatched related bone marrow or unrelated double umbilical cord blood grafts. *Blood*. 2011;118(2):282–8.
- [80] Eapen M, Rocha V, Sanz G, Scaradavou A, Zhang MJ, Arcese W, Sirvent A, Champlin RE, Chao N, Gee AP, Isola L, Laughlin MJ, Marks DI, Nabhan S, Ruggeri A, Soiffer R, Horowitz MM, Gluckman E, Wagner JE; Center for International Blood and Marrow Transplant Research; Acute Leukemia Working Party Eurocord (the European Group for Blood Marrow Transplantation); National Cord Blood Program of the New York Blood Center. Effect of graft source on unrelated donor haemopoietic stem cell transplantation in adults with acute leukaemia: a retrospective analysis. *Lancet Oncol*. 2010;11(7):653–60.
- [81] Windrum P, Morris TC, Drake MB, Niederwieser D, Ruutu T. Variation in dimethyl sulfoxide use in stem cell transplantation: a survey of EBMT centres. *Bone Marrow Transplant*. 2005 Oct;36(7):601–3.
- [82] Morris C, de Wreede L, Scholten M, Brand R, van Biezen A, Sureda A, Dickmeiss E, Trneny M, Apperley J, Chiusolo P, van Imhoff GW, Lenhoff S, Martinelli G, Hentrich M, Pabst T, Onida F, Quinn M, Kroger N, de Witte T, Ruutu T; Chronic Malignancies and Lymphoma Working Parties of EBMT. Should the standard dimethyl sulfoxide concentration be reduced? Results of a European Group for Blood and Marrow Transplantation prospective noninterventional study on usage and side effects of dimethyl sulfoxide. *Transfusion*. 2014 Oct;54(10):2514–22.
- [83] Abbruzzese L, Agostini F, Durante C, Toffola RT, Rupolo M, Rossi FM, Lleshi A, Zanolin S, Michieli M, Mazzucato M. Long term cryopreservation in 5% DMSO maintains unchanged CD34(+) cells viability and allows satisfactory hematological engraftment after peripheral blood stem cell transplantation. *Vox Sang*. 2013 Jul;105(1):77–80.
- [84] Smagur A, Mitrus I, Giebel S, Sadus-Wojciechowska M, Najda J, Kruzel T, Czerw T, Gliwinska J, Prokop M, Glowala-Kosinska M, Chwieduk A, Holowiecki J. Impact of different dimethyl sulphoxide concentrations on cell recovery, viability and clonogenic potential of cryopreserved peripheral blood hematopoietic stem and progenitor cells. *Vox Sang*. 2013 Apr;104(3):240–7.
- [85] Keung YK, Lau S, Elkayam U, Chen SC, Douer D. Cardiac arrhythmia after infusion of cryopreserved stem cells. *Bone Marrow Transplant* 1994;14:363–7.

- [86] Stroncek DF, Fautsch SK, Lasky LC, Hurd DD, Ramsay NK, McCullough J. Adverse reactions in patients transfused with cryopreserved marrow. *Transfusion*. 1991;31:521–6.
- [87] Sputtek A, Jetter S, Hummel K, Kühnl P. Cryopreservation of peripheral blood progenitor cells: characteristics of suitable techniques. *Beitr Infusionsther Transfusionsmed*. 1997;34:79–83.
- [88] Dijkstra-Tiekstra MJ, Setroikromo AC, Kraan M, Gkoumassi E, de Wildt-Eggen J. Optimization of the freezing process for hematopoietic progenitor cells: effect of pre-cooling, initial dimethyl sulfoxide concentration, freezing program, and storage in vapor-phase or liquid nitrogen on in vitro white blood cell quality. *Transfusion*. 2014 Dec;54(12):3155–63.
- [89] Valeri CR, Pivacek LE. Effects of the temperature, the duration of frozen storage, and the freezing container on in vitro measurements in human peripheral blood mononuclear cells. *Transfusion*. 1996;36:303–8.
- [90] Rubinstein P, Dobrila L, Rosenfield RE, Adamson JW, Migliaccio G, Migliaccio AR, Taylor PE, Stevens CE. Processing and cryopreservation of placental/umbilical cord blood for unrelated bone marrow reconstitution. *Proc Natl Acad Sci U S A*. 1995 Oct 24;92(22):10119–22.
- [91] Harris DT, Schumacher MJ, Rychlik S, Booth A, Acevedo A, Rubinstein P, Bard J, Boyse EA. Collection, separation and cryopreservation of umbilical cord blood for use in transplantation. *Bone Marrow Transplant*. 1994;13:135–143.
- [92] Bertolini F, Corsini C, Lauri E, Gorin F, Sirchia G. *J Hematother*. 1993;2:233–234.
- [93] Pahwa RN, Fleischer A, Than S, Good RA. *Proc Natl Acad Sci U S A* 1994;91:4485–4488.
- [94] Rubinstein P, Carrier C, Scaradavou A, Kurtzberg J, Adamson J, Migliaccio AR, Berkowitz RL, Cabbad M, Dobrila NL, Taylor PE, Rosenfield RE, Stevens CE. Outcomes among 562 recipients of placental-blood transplants from unrelated donors. *N Engl J Med*. 1998 Nov 26;339(22):1565–77.
- [95] Selves P, Mirabet V, Roig R. Volume reduction in routine cord blood banking. *Curr Stem Cell Res Ther*. 2010 Dec;5(4):362–6. Review.
- [96] Selves P, Planelles D, Mirabet V, Blanquer A, Carbonell-Uberos F. Qualitative and quantitative cell recovery in umbilical cord blood processed by two automated devices in routine cord blood banking: a comparative study. *Blood Transfus*. 2013 Jul;11(3):405–11.
- [97] Antoniewicz-Papis J, Lachert E, Woźniak J, Janik K, Łętowska M. Methods of freezing cord blood hematopoietic stem cells. *Transfusion*. 2014 Jan;54(1):194–202.

- [98] Yang H, Pidgorna A, Loutfy MR, Shuen P. Effects of interruptions of controlled-rate freezing on the viability of umbilical cord blood stem cells. *Transfusion*. 2015 Jan; 55(1):70–8.
- [99] Broxmeyer HE, Srour EF, Hangoc G, Cooper S, Anderson SA, Bodine DM. High-efficiency recovery of functional hematopoietic progenitor and stem cells from human cord blood cryopreserved for 15 years. *Proc Natl Acad Sci U S A*. 2003 Jan 21;100(2): 645–50.
- [100] Goodwin HS, Grunzinger LM, Regan DM, McCormick KA, Johnson CE, Oliver DA, Mueckl KA, Alonso JM 3rd, Wall DA. Long term cryostorage of UC blood units: ability of the integral segment to confirm both identity and hematopoietic potential. *Cytotherapy*. 2003;5(1):80–6.
- [101] Mitchell R, Wagner JE, Brunstein CG, Cao Q, McKenna DH, Lund TC, Verneris MR. Impact of long-term cryopreservation on single umbilical cord blood transplantation outcomes. *Biol Blood Marrow Transplant*. 2015 Jan;21(1):50–4.

