iMedPub Journals
Our Site: http://www.imedpub.com/

TRANSLATIONAL BIOMEDICINE

2013
Vol. 4 No. 2:2
doi: 10.3823/441

Comparing sources of stem cells for transfusion in acute myeloid leukemia

Paul Faduola

1 Clinical Embryologist/Stem cell scientist Nordica Fertility Centre, Lagos.

* Corresponding Author:
paul@nordicalagos.org

Abstract

Stem cell transfusion have undeniable benefits for patients with Acute Myeloid Leukemia (AML) especially for augmenting the mostly suppressed normal precursor stem cell necessary for fighting infections. While many patients use own stem cells, other patients that might benefit from this treatment are unable to use own stem cells and may lack Human Leucocyte Antigen (HLA) identical donor because of HLA polymorphism. Stem cells collected from the bone marrow , umbilical cord blood and peripheral blood stem cells may be from own or HLA partially mismatched unrelated or related donors. The data obtained show that hematologic recovery is highest in peripheral blood and lower in cord blood than in bone marrow, graft versus host disease is higher in peripheral blood than in bone marrow and lowest in cord blood, incidence of relapse and survival were comparable across sources , mortality is higher in cord blood than in peripheral blood and bone marrow and is mostly as a result of infection due to poor engraftment .This comparison is aimed at improving the quality of decision taking on source of stem cells for transfusion in cases of AML as it compares cord blood, peripheral blood and bone marrow in a single study .

Keywords: Acute Myeloid leukemia (AML),Stem cell transfusion, Hematopoietic stem cells, cord blood, peripheral blood, bone marrow, graft versus host disease, relapse, mortality, survival.

Introduction

Acute Myeloid Leukemia (AML) is the prevalent form of acute leukemia in adults with about 13,000 new cases diagnosed each year in America with children accounting for less than 10 percent(1). The subtypes of AML are diagnosed by examining blood and bone marrow samples for leukemic cells and the cytogenetic changes in the cells (2). This diagnosis is necessary for treatment decision because in AML, the precursor stem cells that are formed are abnormal and so cannot differentiate into normal white blood cells that fights infection(3). A typical treatment plan in AML include chemotherapy , stem cell transfusion, all-trans retinoic acid (ATRA) and other newer treatments approved or in clinical trials(4) .Stem cell transfusion is increasingly playing a critical role in AML treatment because the myeloid blast are not functional and needs to be augmented to fight infections(5). However it is still not clear which of the treatment option is best for consolidation, treatment decisions for patients with AML should be made on a case by case basis taking into consideration age, health and other factors.

In AML, chemotherapy is the first- line of treatment, it is aimed at inducing a remission which may be followed by another chemotherapy or stem cell transfusion to restore the bone marrow function in the patients. These cells may be harvested from the patient (autologous) or from a donor (allogeneic). Depending on the site of harvest, the sources of stem cell for AML therapy may include bone marrow(BM),peripheral blood(PB) or cord blood(CB) (6).

Complications may arise from stem cell transfusion which could affect the outcome of the treatment with the early ones being associated with the effects of the preparative

regimen used and may include mucositis, hemorrhagic cystitis and hepatic veno-occlusive disease(7).Others are acute and chronic GVHD caused by the donors mature T- lymphocytes, infections mainly caused by prolonged pancytopenia, relapse and mortality.(8,9)

Despite this shortcomings, stem cell transfusion is increasingly being used for patients with more aggressive forms of AML, those who have had a relapse following remission, and those who do not achieve remission after initial induction therapy(5).

Technological advances have resulted in improved HLA typing and good GHVD management, these advances together with the establishment of more cord blood banks and recent data showing comparable result of cord blood to other sources of stem cell have left a fair options for selection. This study is one of the few that aim to compare bone marrow, peripheral and cord blood stem cells specifically for AML patients.

Bone Marrow

Majority of hematopoietic stem cells(HSC) are resident in the bone marrow which has made HSC synonymous to bone marrow(10). Stem cells from bone marrow can be transfused as autologous or allogeneic (11) . Allogeneic transfusion is indicated in patients in second remission and in untreated first relapse but patients transfused in first remission achieve better outcome(7). Autologous transfusion are offered to older patients and in patients in first remission and as a therapeutic option in second remission (12). Results from randomized studies in patients that were transfused with bone marrow and those that received chemotherapy alone have been mixed with some showing promise while others show no superior advantage in the outcome(13-17).

Peripheral Blood

The subcutaneous injections of Granulocyte-colony stimulating factor to mobilize stem cells from the patient or donor's bone marrow into the peripheral circulation has made peripheral blood the most common source of stem cell for transfusion (18). Mobilized peripheral blood is now replacing bone marrow, as harvesting peripheral blood stem cells (PBSCs) is easier than harvesting bone marrow stem cells (19). A randomized study show a relapse advantage and comparable survival rate of PBSC over chemotherapy as post remission therapy(20)

Cord Blood

Cord blood is increasingly becoming an important source of hematopoietic stem cells. The increase in number of cord blood banks have opened options for cord stem cells to be stored for individual, family or for public use after it is harvested(21).The advantages of cord blood stem cells are the availability, ease of harvest, and the reduced risk of graft-versus-host-disease (GVHD). It use however , have been limited by the less number of cells that can be harvested and the delayed immune reconstitution, which leaves patients vulnerable to infections for a longer period of time(22-23). Large number of children with AML have benefitted from CB transfusion and they are increasingly being used in adults when matched unrelated donor or a haploidentical donor are not available with some promising result (24-27).

Comparison

Hematopoietic recovery

After stem cell transplantation, successful engraftment is determined by performing daily blood cell counts. Neutrophils and platelets are commonly used markers of hematopoietic recovery, an absolute neutrophil count (ANC) of at least 500 for three days in a row and platelet count of 20,000 - 50,000 are required to establish engraftment (28)).Many randomized and meta-analysis studies have shown superior hematopoietic recovery in peripheral blood (PBSC) more than in bone marrow(BM), with days for recovery of neutrophils ranging from 12-35 in PBSC and 13-68 in BM while platelets recover at a median time of 16days for PBSC and 23 days for BM(29-35).Cord blood(CB) hematopoietic recovery is slow compared to BM and PB (36-41).This delayed engraftment in CB has been linked to lower doses of nucleated cell count in single CB donation compared to BM/ PB and have raised concerns about successful engraftment in adults with larger body weight (42).Studies are being done to address this challenge, one being the use of double cord blood units instead of single unit to achieve a human leukocyte antigen (HLA) matching 6/6 and a nucleated cell dose of more than 3×10^6 cells/ kg (43).

Graft versus host disease.

The source of stem cell for AML patients have influence on the risk of GVHD (21).A small increase in the risk of acute GVHD after PBSCT over BM have been reported in cohort studies while randomized studies fail to show any significant increase (34,44,45,46,47,48,49,50).PBSC have been linked to significant increase in risk of chronic GHVD but not acute GVHD(51-54). Concerns about larger concentration of mature, immune-competent T cells that could increase the risk of GVHD have necessitated comparative studies on T- cell depleted sources over non T- cell depleted sources with results showing significant decrease in GVHD in depleted sources

but with high level of graft rejection (55-56).Less graft rejection and better GVL response has been achieved using reduced level of T – cell below 100% (57) but studies involving selective purging of CD 8 T- cell have been most promising(58).CB have low risk of acute and chronic graft versus host disease (GVHD) even with broader HLA disparity than PBSC/ BM(39,59), this may be due to the fewer number and immunological naïve CB-derived T cells thus making it preferable to T- cell depleted sources. There is also a preserved graft versus leukemia (GVL) effect In CB due to higher number and unique properties of NK cells in CB grafts(39).

Relapse

Animal studies showed a lower relapse rate with PBSC than with BM(60) but only few human reports have confirmed this low relapse in PBSC compared to BM (34,61,62) .PBSC and BM have been reported in many studies to be comparable in terms of relapse rate (59,63,64) with only one study reporting higher relapse with PBSC than BM (69) but the high relapse rate reported might be due to bias selection with regards to risk profile. No significant difference in the risks of relapse in CB compared to BMT/PBSCT was recorded (65,66).

Mortality

Deaths from stem cell transfusion commonly results from GVHD and infection among other causes. Depending on the cause, the time of death occurred at a median of 3 months with a range of 0 to 200 months(67). Some studies have recorded lower transplantation related mortality in PBSC than BM in Myelodysplastic syndromes (MDS) (68) and in certain subtype of leukemia(69) while a comparable outcome was reported in a meta-analysis study(62).There are attempts to link the increased risk of chronic GVHD in PBSC to the high mortality in early stage of AML as against the lower mortality rate in the more advanced acute leukemia (70).CB has increase risk of mortality compared to BM/PBSC (40),reduced mortality rate was reported in patients with higher dose of $CD34^+$ CB (21).Most of the deaths in CB were caused by infection and may be due to delayed hematopoietic engraftment. Sequential cord blood transplantation, cord blood expansion and combination cord blood and haploidentical stem cell transplants are Strategies being tried to reduce mortality in cord blood with promising results(21,71,72).

Survival

Many studies have reported overall survival and leukemia-free survival to be nearly identical for patients grafted with unrelated donor PBPCs or BM(31,73,74,75,76).Some have showed superior overall survival in PBSC compared to BM in advanced stage of acute leukemia patients in second remission(51,61,77) but fail to establish any significant difference in survival in early stage of the disease with either sources (65). Comparable survival in CB and PBSC/ BM among standard-risk and high-risk groups have also been recorded(41,78 ,79). The comparable survival reported in CB were in double cord blood transplants and young patients which might have contributed to the better rate.

Conclusion

Several factors could influence the outcome of stem cell transfusion for AML treatment, knowing the benefit and risk of the sources of stem cells is critical in taking informed decision.

Reference

1. Jamieson K and Odenike O(2012) .Late-phase investigational approaches for the treatment of relapsed/refractory acute myeloid. leukemia.Expert Opinion on Pharmacotherapy.2012; 13:15, 2171-2187
2. Jennings CD, Foon KA (2007).Recent advances in flow cytometry: application to the diagnosis of hematologic malignancy. Blood. 90(8):2863-92.
3. Gocek E and Marcinkowska E (2011). Differentiation Therapy of Acute Myeloid Leukemia. Cancers 3, 2402-2420; doi:10.3390/ cancers3022402
4. Estey EH (2009). Treatment of acute myeloid leukemia. Haematologica. 94(1): 10–16. doi: 10.3324/haematol.2008.001263.
5. Cornelissen J J and Löwenberg B (2005) Role of Allogeneic Stem Cell Transplantation in Current Treatment of Acute Myeloid Leukemia. ASH Education Book vol. 2005 no. 1 151-155
6. Faduola P(2012) Stem cell transplantation in acute myeloid leukemia:history,drivers and challenges. Int J Biol Med Res. 3(3):2132-2137
7. Lee J H, Choi J, Kwon K A, Lee S, Oh S Y et al (2010). Fludarabine-based myeloablative regimen as pre-transplant conditioning therapy in adult acute leukemia/ myelodysplastic syndrome: comparison with oral or intravenous busulfan with cyclophosphamide. Korean J Hematol 45(2): 102–108.
8. Jacopo P and Fabio C(2010) Allogeneic stem cell transplantation for acute myeloid leukemia. haematol vol. 95 no. 6 857-859
9. Pallera A M, and Schwartzberg L S (2004) Managing the Toxicity of Hematopoietic Stem Cell Transplant. J Support Oncol 2:223–247
10. Mercier FE, Ragu C & Scadden D T(2012) The bone marrow at the crossroads of blood and immunity. Nature Reviews Immunology 12, 49-60 doi:10.1038/nri3132
11. Bjorkstran BB , Ljungman P, Svensson H,Hermans J, Alegre A et al (1996) Allogeneic bone marrow transplantation versus autologous stem cell transplantation in multiple myeloma: a retrospective case-matched study from the European Group for Blood and Marrow Transplantation.Blood .88: 4711-4718
12. Peters WP, Hamm C, Baynes RD. Autologous Bone Marrow and Stem Cell Transplantation. In: Bast RC Jr, Kufe DW, Pollock RE, et al., editors. Holland-Frei Cancer Medicine. 5th edition. Hamilton (ON): BC Decker; 2000. Chapter 67. Available from: http://www.ncbi.nlm.nih.gov/ books/NBK20890/
13. Burnett AK, Goldstone AH, Stevens RM, et al(1998) Randomized comparison of addition of autologous bone-marrow transplantation to intensive chemotherapy for acute myeloid leukemia in first remission: results of MRC AML 10 trial. UK Medical Research Council Adult and Children's Leukemia Working Parties. Lancet 351 (9104):700-708.
14. Zittoun RA, Mandelli F, Willemze R, et al(1995) Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia: European Organization for Research and Treatment of Cancer (EORTC) and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Leukemia Cooperative Groups. N Engl J Med 332(4):217-223
15. Woods WG, Neudorf S, Gold S, et al(2001) A comparison of allogeneic bone marrow transplantation, autologous bone marrow transplantation, and aggressive chemotherapy in children with acute myeloid leukemia in remission: a report from the Children's Cancer Group. Blood 97(1):56-62
16. Harousseau JL, Cahn JY, Pignon B, et al(1997) Comparison of autologous bone marrow transplantation and intensive chemotherapy as postremission therapy in adult acute myeloid leukemia. Blood 90(8):2978-2986
17. Cassileth PA, Harrington DP, Appelbaum FR, et al(1998) Chemotherapy compared with autologous or allogeneic bone marrow transplantation in the management of acute myeloid leukemia in first remission. N Engl J Med 339(23):1649-1656
18. Montgomery M, and Cottler-Fox M(2007) Mobilization and Collection of Autologous Hematopoietic Progenitor/Stem Cells. Clinical Advances in Hematology & Oncology Volume 5, Issue 2
19. D.F. Stroncek, D.L. Confer, and S.F. Leitman(2000) Peripheral blood progenitor cells forHPC transplants involving unrelated donors. TRANSFUSION 40:731-741.
20. Vellenga E, Putten WV, Ossenkoppele GJ, Verdonck LF, Theobald M et al (2011) Autologous peripheral blood stem cell transplantation for acute myeloid leukemia. Blood First Edition Paper, prepublished online September 27, 2011; DOI 10.1182/blood-2011-07-370247
21. Ballen KK(2005) New trends in umbilical cord blood transplantation. Blood vol. 105 no. 10, 3786-3792
22. Will AM (1999) Umbilical cord blood transplantation.Arch Dis Child 80:3-6 doi:10.1136/adc.80.1.3
23. Gluckman E, Rocha V(2008) Indications and results of cord blood transplant in children with leukemia. Bone Marrow Transplant. 41 Suppl 2:S80-2.
24. Wall DA, Carter SL, Kernan NA, et al(2005) Busulfan/melphalan/ antithymocyte globulin followed by unrelated donor cord blood transplantation for treatment of infant leukemia and leukemia in young children: The Cord Blood Transplantation study (COBLT) experience. Biol Blood Marrow Transplant 11:637-646.
25. Laughlin MJ, Barker J, Bambach B, et al.(2001) Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. N Engl J Med 344:1815-1822.
26. Brunstein CG, Baker KS, Wagner JE(2007) Umbilical cord blood transplantation for myeloid malignancies. Curr Opin Hematol 14:162-169.
27. Eapen M, Rubinstein P, Zhang MJ, et al.(2007) Outcomes of transplantation of unrelated donor umbilical cord blood and bone marrow in children with acute leukaemia: A comparison study. Lancet 369:1947-1954
28. Migliaccio AR, Adamson JW, Stevens CE, Dobrila NL, CM Carrier et al (2000) 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. 96(8):2717-22.
29. Mahmoud H, Fahmy O, Kamel A, Kamel M, El-Haddad A et al(1999) Peripheral blood vs bone marrow as a source for allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 24(4):355-8.
30. Pavletic ZS, Bishop MR,Tarantolo SR, Martin-Algarra S, Bierman PJet al (1997) Hematopoietic recovery after allogeneic blood stem-cell transplantation compared with bone marrow transplantation in patients with hematologic malignancies. JCO vol. 15 no. 4 1608-1616
31. Ghavamzadeh A, Iravani M, Ashouri A, Mousavi SA, Mahdavi N et al (2008) Peripheral blood versus bone marrow as a source of hematopoietic stem cells for allogeneic transplantation in children with class I and II beta thalassemia major. Biol Blood Marrow Transplant. 14(3):301-8.
32. Arai S, Klingemann HG(2003) Hematopoietic stem cell transplantation: bone marrow vs. mobilized peripheral blood. Arch Med Res. 34(6):545-53.
33. Couban S, Simpson DR, Barnett MJ, Bredeson C, Hubesch L et al (2002) A randomized multicenter comparison of bone marrow and peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. Blood100(5):1525-31
34. U¨ stu¨n C, ArslanO¨ , Beksac¸ M, et al(1999) A retrospective comparison of allogeneic peripheral blood stem cell and bone marrow transplantation results from a single center: A focus on the incidence ofgraft-vs.-host disease and relapse. Biol Blood Marrow Transplant 5:28-35,
35. Stem Cell Trialists' Collaborative Group.Allogeneic Peripheral Blood Stem-Cell Compared WithBone Marrow Transplantation in the Management of Hematologic Malignancies: An Individual Patient Data Meta-Analysis of Nine Randomized Trials. J Clin Oncol 23:5074-5087
36. Takahashi S, Ooi J, Tomonari A, Konuma T, Tsukada N et al (2004) Single-institute comparative analysis of unrelated bone marrow transplantation and cord blood transplantation for adult patients with hematologic malignancies. Blood, vol. 104 no. 12 3813-3820
37. Konuma T and Takahashi S. Cord Blood Transplantation in Adults with Acute Leukemia. Acute Leukemia - The Scientist's Perspective and Challenge, ISBN: 978-953-307-553-2

38. Takahashi S, Ooi J, Tomonari A, Konuma T, Tsukada N et al (2007) Comparative single-institute analysis of cord blood transplantation from unrelated donors with bone marrow or peripheral blood stem-cell transplants from related donors in adult patients with hematologic malignancies after myeloablative conditioning regimen. Blood.;109(3):1322-30.
39. Stanevsky A et al(2009) Umbilical cord blood transplantation: Pros, cons and beyond. Blood Reviews . doi:10.1016/j.blre.
40. Rocha V, Cornish J, Sievers EL, Filipovich A, Locatelli F et al (2001). Comparison of outcomes of unrelated bone marrow and umbilical cord blood transplants in children with acute leukemia. Blood. 97(10):2962-71.
41. Rocha V, Labopin M, Sanz G, Arcese W, Schwerdtfeger R et al (2004). Transplants of umbilical-cord blood or bone marrow from unrelated donors in adults with acute leukemia. N Engl J Med 351, 2276–2285.
42. Broxmeyer, H.E., Cord blood hematopoietic stem cell transplantation (2010) StemBook, ed. The Stem Cell Research Community, StemBook, doi/10.3824/stembook.1.52.1,
43. Doan PL ,Chao NJ(2010) Advances in cord blood transplants in adults. F1000 Med Rep. 2: 12
44. Azevedo WM, Aranha FJP, Gouvea AC, et al(1995) Allogeneic transplantation with blood stem cells mobilized by rhG-CSF for hematological malignancies. Bone Marrow Transplant 16:647-653.
45. Przepiorka D, Anderlini P, Ippoliti C, et al(1997) Allogeneic blood stem cell transplantation in advanced hematologic cancers. Bone Marrow Transplant 19:455-460.
46. Lemoli RM, Bandini G, Leopardi G, et al(1998) Allogeneic peripheral blood stem cell transplantation in patients with early-phase hematologic malignancy: A retrospective comparison of short-term outcome with bone marrow transplantation. Haematologica 83:48-55.
47. Russell JA, Larratt L, Brown C, et al(1999) Allogeneic blood stem cells and bone marrow transplantation for acute myelogenous leukemia and myelodysplasia: Influence of stem cell source on outcome. Bone Marrow Transplant 24:1177-1183.
48. Scott MA, Gandhi MK, Jestice HK, et al(1998) A trend towards an increased incidence of chronic graft-versus-host disease following allogeneic peripheral blood progenitor cell transplantation: A case controlled study. Bone Marrow Transplant 22:273-276.
49. Storek J, Gooley T, Siadak M, et al (1997) Allogeneic peripheral blood stem cell transplantation may be associated with a high risk of chronicgraft-versus-host disease. Blood 90:4705-4709.
50. Russell JA, Brown C, Bowen T, et al (1996) Allogeneic blood cell transplants for haematological malignancy: Preliminary comparison of outcomes with bone marrow transplantation. Bone Marrow Transplant 17:703-708
51. Bensinger WI, Martin PJ, Storer B, et al(2001) Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. N Engl J Med 344:175-181
52. Schmitz N, Bacigalupo A, Hasenclever D, et al (1998) 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. 21:995-1003.
53. Schmitz N, Beksac M, Hasenclever D, et al (2000) A randomised study from the European group for blood and marrow transplantation comparing allogeneic transplantation of Filgrastim-mobilised peripheral blood progenitor cells with bone marrow transplantation in 350 patients (pts) with leukemia. Blood 96:481, 2000 (abstr 2068)
54. Cutler C, Giri S, Jeyapalan S, Paniagua D, Viswanathan A, and Antin JH (2001) Acute and Chronic Graft-Versus-Host Disease After Allogeneic Peripheral-Blood Stem-Cell and Bone Marrow Transplantation: A Meta-Analysis. J Clin Oncol 19:3685-3691.
55. Devine SM, Carter S, Soiffer RJ, Pasquini MC, Hari PN et al (2011) Low Risk of Chronic Graft-versus-Host Disease and Relapse Associated with T Cell–Depleted Peripheral Blood Stem Cell Transplantation for Acute Myelogenous Leukemia in First Remission: Results of the Blood and Marrow Transplant Clinical Trials Network Protocol 0303. Biol Blood Marrow Transplant. 17(9):1343-51
56. Sehn LH, Alyea EP, Weller E,Canning C, Lee S et al (1999) Comparative Outcomes of T-Cell–Depleted and Non–T-Cell–Depleted Allogeneic Bone Marrow Transplantation for Chronic Myelogenous Leukemia: Impact of Donor Lymphocyte Infusion. J Clin Oncol. 17(2):561-8.
57.Link H.(1999) T-cell depletion of allogeneic peripheral blood stem cells. Baillieres Best Pract Res Clin Haematol. 12(1-2):87-98.
58.Elmaagacli AH, Peceny R,Steckel N,Trenschel R, Ottinger H et al (2003) Outcome of transplantation of highly purified peripheral blood CD34$^+$ cells with T-cell add-back compared with unmanipulated bone marrow or peripheral blood stem cells from HLA-identical sibling donors in patients with first chronic phase chronic myeloid leukemia. Blood vol. 101 no. 2 446-453
59. Takahashi S, Ooi J, Tomonari A, Konuma T, Tsukada N et al (2007) Comparative single-institute analysis of cord blood transplantation from unrelated donors with bone marrow or peripheral blood stem-cell transplants from related donors in adult patients with hematologic malignancies after myeloablative conditioning regimen. Blood.109(3):1322-30.
60. Wierenga PK, Setroikromo R, Kamps G, Kampinga HH, Vellenga E (2002) Peripheral Blood Stem Cells Differ from Bone Marrow Stem Cells in Cell Cycle Status, Repopulating Potential, and Sensitivity Toward Hyperthermic Purging in Mice Mobilized with Cyclophosphamide and Granulocyte Colony-Stimulating Factor. J Hematother Stem Cell Res.11(3):523-32.
61. Stem Cell Trialists' Collaborative Group.Allogeneic Peripheral Blood Stem-Cell Compared WithBone Marrow Transplantation in the Management of Hematologic Malignancies: An Individual Patient Data Meta-Analysis of Nine Randomized Trials. J Clin Oncol 23:5074-5087
62. Chang YJ, Weng CL, Sun LX, Zhao YT(2012) Allogeneic bone marrow transplantation compared to peripheral blood stem cell transplantation for the treatment of hematologic malignancies: a meta-analysis based on time-to-event data from randomized controlled trials. Annals of Hematology 91(3): 427-437
63. Ringdén O, Labopin M,Bacigalupo A,Arcese W, Schaefer UW et al.(2002) Transplantation of Peripheral Blood Stem Cells as Compared With Bone Marrow From HLA-Identical Siblings in Adult Patients With Acute Myeloid Leukemia and Acute Lymphoblastic Leukemia. J Clin Oncol.20(24):4655-64
64. Stamatović D, Balint B, Tukić L, Elez M, Tarabar O et al (2011) Impact of stem cell source on allogeneic stem cell transplantation outcome in hematological malignancies. Vojnosanit Pregl. 68(12):1026-32.
65. Gorin NC, Labopin M, Blaise D, Reiffers J, Meloni G et al(2009) Higher Incidence of Relapse With Peripheral Blood Rather Than Marrow As a Source of Stem Cells in Adults With Acute Myelocytic Leukemia Autografted During the First Remission. J Clin Oncol. 27(24):3987-93
66. Atsuta Y, Morishima Y, Suzuki R, Nagamura-Inoue T, Taniguchi S et al(2012) Comparison of Unrelated Cord Blood Transplantation and HLA-Mismatched Unrelated Bone Marrow Transplantation for Adults with Leukemia. Biol Blood Marrow Transplant. 18(5):780-7
67. Gratwohl A,Brand R, Frassoni F, Rocha V, Niederwieser D et al (2005) Cause of death after allogeneic haematopoietic stem cell transplantation (HSCT) in early leukaemias: an EBMT analysis of lethal infectious complications and changes over calendar time. Bone Marrow Transplantation (2005) 36, 757–769. doi:10.1038/sj.bmt.1705140
68. Guardiola P, Runde V, Bacigalupo A, Ruutu T, Locatelli F et al(2002). Retrospective comparison of bone marrow and granulocyte colony-stimulating factor–mobilized peripheral blood progenitor cells for allogeneic stem cell transplantation using HLA identical sibling donors in myelodysplastic syndromes. Blood. 15;99(12):4370-8.
69. Champlin RE, Schmitz N, Horowitz MM, et al.(2000) Blood stem cells compared with bone marrow as a source of hematopoietic cells for allogeneic transplantation. Blood.95:3702-3709.
70. Urbano-Ispizua A, Brunet S, Solano C, et al.(2001) Spanish Group of Allo-PBT. Allogeneic transplantation of CD34+-selected cells from peripheral blood in patients with myeloid malignancies in early

phase: a case control comparison with unmodified peripheral blood transplantation. Bone Marrow Transplant. 28:349–54
71. Petropoulou AD and Rocha V(2011) Risk factors and options to improve engraftment in unrelated cord blood transplantation. Stem Cells Int. 2011: 610514.
72. Hanley PJ, Cruz CR, Shpall EJ, Bollard CM(2010) Improving Clinical Outcomes Using Adoptively Transferred Immune Cells from Umbilical Cord Blood. Cytotherapy. 12(6): 713–720. doi: 10.3109/14653249.2010.517518
73. Remberger M, Ringdén O, Blau IW, Ottinger H, Kremens B et al (2001) No difference in graft-versus-host disease, relapse, and survival comparing peripheral stem cells to bone marrow using unrelated donors. Blood vol. 98 no. 6 1739-1745
74. Gallardo D, de la Cámara R, Nieto JB, Espigado I, Iriondo A et al (2009) Is mobilized peripheral blood comparable with bone marrow as a source of hematopoietic stem cells for allogeneic transplantation from HLA-identical sibling donors? A case-control study. Haematologica. 94(9):1282-8.
75. Liberti G,Pearce R,Taghipour G,Majolino I and Goldstone AH(1994) Comparison of peripheral blood stem-cell and autologous bone marrow transplantation for lymphoma patients: A case-controlled analysis of the EBMT Registry data. Ann Oncol 5 (suppl 2): S151-S153.
76. Chang YJ, Weng CL, Sun LX, Zhao YT(2012) Allogeneic bone marrow transplantation compared to peripheral blood stem cell transplantation for the treatment of hematologic malignancies: a meta-analysis based on time-to-event data from randomized controlled trials. Ann Hematol. 91(3):427-37. doi: 10.1007/s00277-011-1299-8.
77. Simpson DR, Couban S, Bredeson C, et al(2000) A Canadian randomized study comparing peripheral blood (PB) and bone marrow (BM) in patients undergoing matched sibling transplants for myeloid malignancies [abstract]. Blood. 96:481.
78. Jacobson CA,Turki AT,McDonough SM, Stevenson KE,Kim HT et al (2012) Immune Reconstitution after Double Umbilical Cord Blood Stem Cell Transplantation: Comparison withUnrelated Peripheral Blood Stem Cell Transplantation. Biol Blood Marrow Transplant. 18:565-574
79. Chen YB, Aldridge J, Kim HT, Ballen KK, Cutler C et al (2012) Reduced-Intensity Conditioning Stem Cell Transplantation: Comparison of Double Umbilical Cord Blood and Unrelated Donor Grafts. Biol Blood Marrow Transplant. 18(5):805-12