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Review Article

Peripheral blood stem cells: mobilization strategies and potential therapeutic applications

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ABSTRACT

Peripheral blood stem cell (PBSC) transplantation is now a day's preferred transplantation source of stem cells as treatment modality for various hematologic malignancies. Progenitor hematopoietic stem cells express CD34 antigen, through which PBSCs are selected and collected. Peripheral blood stem cells provide a rapid and effective hematopoietic recovery after administration in patients having hematological ailments, with the advantages of a shorter engraftment time and the lack of a need for surgical procedure necessary for bone marrow harvesting. PBSCs are routinely present in blood circulation; though number too low to be used for transplantation. PBSCs can be mobilized by the administration of G-CSF or GM-CSF alone or preceded by chemotherapy. The yield of stem cells after mobilization differ enormously with disease condition, age etc. and several studies have been performed with different mobilizing regimen and factors affecting yield of progenitor cells. Mobilized peripheral blood stem cells have been increasingly used clinically for many diseases including myeloma, leukemia, lymphoma etc. In the current review, we give brief introduction about peripheral blood stem cells, its advantages over bone marrow and emphasize on different mobilizing strategy used for mobilizing PBSCs and expansion of these PBSCs under in vitro environment. The potential clinical application of PBSCs in treating different diseases has also been reviewed here in detail.

Keywords: Mobilization, PSBC, Stem cell transplant

INTRODUCTION

Millions of people suffering from degenerative diseases worldwide can be cured through organ and tissue replacement; however, dearth of donors limits their usage and led to development of cell based therapeutics. Stem cells hold great promise for regenerative medicine because of their self-renewal and multi-lineage differentiation potential. Stem cells are unspecialized cells having ability to renew themselves for longer period of time without change in their properties. Stem cells obtained from various adult tissues such as bone marrow, adipose tissues, umbilical cord, dental pulp, peripheral blood etc. have advantages of easy accessibility, homing ability, and non-tumorigenic nature in comparison to embryonic stem cells. Immunomodulatory properties of stem cells make them attractive candidate to be used in cell therapy to treat many degenerative disorders. Hematopoietic stem cells present in bone marrow are routinely used for treating hematologic diseases like

multiple myeloma, lymphoma, thalassemia etc. The circulating CD34+ stem cells are present in blood circulation also; however, their number is too small to be used for clinical transplantation. With the advent of growth factors and mobilization techniques, peripheral blood stem cells (PBSCs) have witnessed dramatic increase in its usage for treating hematologic malignancies. Peripheral blood stem cells (PBSCs) have become promising alternative to bone marrow grafting in last two decades and replaced bone marrow transplant to a large extent.[1]

Benefits of PBSCs over bone marrow transplantation have been studied.[2-5] The number of CD34+ hematopoietic progenitor cells were higher in PB stem cell graft, faster reconstitution of neutrophils and platelets, no difference in graft versus host diseases were observed. Champlin and Bensinger et al. reported rapid recovery of platelets and neutrophils compared with marrow transplant.[6-7] PBSCs transplantation was found successful in pediatric patients too with fewer complications. Associated advantages and disadvantages with bone marrow and peripheral blood are summarized in Table - 1

Table 1: Advantages and disadvantages of bone marrow and peripheral blood derived stem cells.

Source	Advantages	Disadvantages
Bone Marrow	• Cytokine usage not necessary • Single collection • No need to catheter	• Needs general anesthesia • Morbidity and mortality rate higher • Slow engraftment
Peripheral Blood	• Does not require anesthesia • Safe and donor friendly collection procedure • Faster hematopoietic engraftment • Lower rate of morbidity and mortality • Convenient source of stem cell collection	• Collection may take several days • Haemorrhage, infection are possible complications

Peripheral Blood stem cell Transplant

Peripheral blood stem cell transplant is not a day care procedure; rather involves various steps listed below (Figure 1).

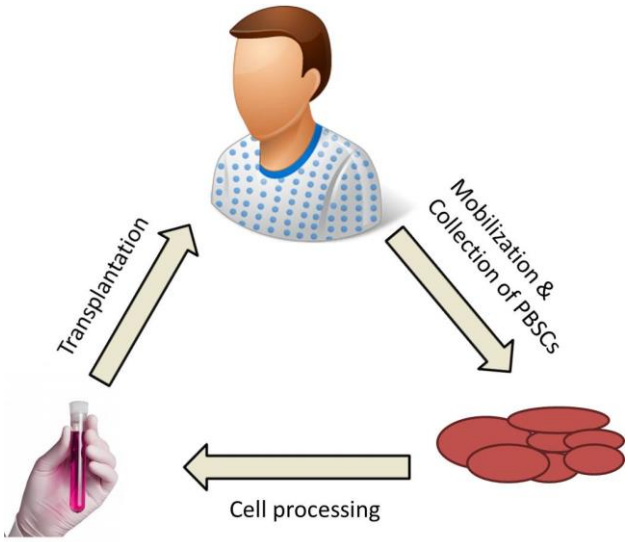

Figure 1: Steps involved in peripheral blood stem cell transplant.

- Mobilization- Administration of mobilizing agent and cell mobilization
- Collection- Collection of mobilized cells
- Product preparation- Cell processing for storage
- Transplantation- Administration of preparative regimen and cell transplant either autogenic or allogenic
- Engraftment and recovery.[8-10]

Mobilization strategies -Different mobilizing agents

Mobilization is recruitment of progenitor stem cells into peripheral blood from bone marrow following treatment with chemotherapy and or cytokine. Research in mobilization methods continues to optimize cytokine regimen, collection of targeted stem cell dose, minimize the number of apheresis session, and have cost effective approach. Today variety of mobilization strategies have been used including either cytokine alone or in combination of chemotherapy followed by cytokine administration.

CHEMOTHERAPY

The first mechanism discovered to mobilize stem cells from bone marrow was chemotherapy. It was observed that chemotherapy used during acute leukemia resulted in around 50 fold increase in number of hematopoietic stem cells and collection and administration of these cells had rapid engraftment.[11] To have adequate amount of cells, different chemotherapeutic agents such as cyclophosphamide, etoposide, ifosfamide, cisplatin, cytarabine etc. are used either alone or in combination.[12-15] The associated disadvantages with chemo mobilization are unpredictable apheresis timing, need of hospitalization, risk of neutropenia and high cost. Earlier stem cell mobilization method relies on chemotherapy

alone since the discovery of G-CSF which exhibited 1000-fold increase in number of stem cells.

Cytokine

Cytokine priming has emerged as an efficient and acceptable method for hematopoietic stem cell mobilization from extravascular bone marrow sites to blood. Cytokines are small secreted proteins, produced in response to immune stimulus and regulate immunity, inflammation, hematopoiesis and cellular function such as proliferation, activation, and secretion of effectors molecules. Studies are continuously done on various cytokine molecules and on factors which influence cell mobilization - age of patient, type and dose of cytokine used, combination with chemotherapy.[16]

Recombinant human granulocyte-colony stimulating factor (rhG-CSF)

The most preferred cytokine for PBSCs mobilization is rhG-CSF. In common practice, G-CSF is administered for 4 days and PBSCs are collected by apheresis from 5th day onwards. G-CSF is commonly administered at a dose of at-least 10µg/kg/day for 4-5 days to have 5x106 CD34+ cells per kg of body for rapid engraftment of platelets and neutrophils. A dose response relationship was observed between rhG-CSF dose and degree of mobilization CD34+ progenitor cells up to 10-16µg/kg/day. G-CSF mobilized peripheral blood stem cells demonstrated better engraftment, faster neutrophils and platelets recovery, faster lymphocyte reconstitution and lower mortality rate as compared to bone marrow or umbilical cord blood.[17-18]

Transplantation of allogenic PBSCs also exhibited rapid hematologic recovery with low incidence of acute graft versus host disease. However poor mobilization was observed with G-CSF in patients with multiple myeloma, lymphoma, leukemia, cancer patients and requires extended apheresis.[19-22] These mobilization failures led to search for novel agents and approaches for stem cell mobilization. The side effects associated with G-CSF administration are spontaneous splenic rupture, thrombosis and flare of autoimmune disease.[23-24]

Mobilization with disease specific chemotherapy plus G-CSF is an effective approach for PBSCs mobilization in patients who need salvage therapy. Mobilization with chemotherapy plus G-CSF exhibited 2 to 6 fold higher yield of cells in comparison to G-CSF alone.

Alternate mobilizing agents

Different cytokines are under investigation to improve stem cell collection from peripheral blood.25-26

GM-CSF (Granulocyte-macrophage colony stimulating factor)

GM-CSF is also an approved mobilizing agent for PBSCs immobilization.[27-29] GM-CSF administration decrease mobilization of T cells and natural killer cells and increase mobilization of CD4+CD25+ cells.[30-31] To have adequate CD34+ cells, higher dose of GM-CSF is needed which restricts its usage in practice.

Recombinant human erythropoietin (EPO)

EPO has demonstrated improvement in mobilization efficiency of G-CSF with higher number of CD34+ cells with lower apheresis in comparison to G-CSF alone. The febrile neutropenia attack, antibiotic dosage, hospital stay was shortened in the G-CSF plus EPO therapy. However, benefits of EPO were not reproducible in randomized studies.[32-36]

Stem cell factor (SCF)

SCF has also demonstrated stimulation of progenitor cells to blood from marrow. Limited reports are present with alone recombinant SCF, its usage has been reported with other cytokines in literature. Recombinant human SCF combined with filgrastim administration exhibited persistence of CD34+ cells for longer time (13 days) in comparison to filgrastim alone (7 days).[37-40] SCF combined with G-CSF showed benefits as mobilization strategy in patients suffering with hematological disease, indole lymphoproliferative disease or solid tumors.[41-43] However US Food and Drug Administration (FDA) has not approved its usage due to occasional occurrence of anaphylactic reactions, though approved in Australia, New Zealand and Canada combined with filgrastim.

Recombinant human TPO (rhTPO)

rhTPO is glycosylated molecule which has shown its efficacy in mobilization of progenitor cells in patients with breast cancer and hemalogical malignancies.[44-47] Disadvantages with TPO are intravenous administration, delayed action, risk of thrombocytosis.

Pegfilgrastim (Pegylated G-CSF)

Pegylated G-CSF has also been widely explored for PBSCs mobilization. Chemotherapy followed by pegfilgrastim exhibited sufficient number of mobilized PBSCs in patients having Plasma Cell Myeloma (PCM) and lymphoma.[48-52] The patients mobilized with pegfilgrastim demonstrated CD34+ cell collection in fewer apheresis and even apheresis started 2 days earlier. Higher number of CD34+ cells was observed with pegfilgrastim in comparison to filgrastim in PCM patients. Single dose of 12 mg pegfilgrastim without chemotherapy was found successful in PCM patients; however, dose of 100 or 300µg/kg pegfilgrastim was shown to induce sufficient number of CD34+ cells.[53-54] The larger plasma half-life of pegfilgrastim in comparison to G-CSF allows single dose of pegfilgrastim to be clinically effective. The adverse reactions

associated with pegfilgrastim are similar to G-CSF; commonest is bone pain and occurrence range is 3-20%. The earlier start of apheresis, reduction in number of apheresis, rapid leukocyte recovery may have positive effect on patient compliance but mobilization with 12 mg pegfilgrastim is not cost-effective approach.

Plerixafor

Plerixafor functions by antagonizing the binding of the chemokine Stromal Cell-Derived Factor-1 (SDF-1) to its cognate receptor CXCR4 and results in the rapid mobilization of hematopoietic stem cells into the peripheral circulation.

With subcutaneous injection, plerixafor is rapidly absorbed reaching peak concentrations in 30–60 min, and results in rapid increase in peripheral blood CD34+ cells in healthy donors. It has a half-life of 3-5 hours in patients having normal renal function and gets eliminated unchanged in urine. The linear kinetics has been exhibited with plerixafor doses of 40–240mg/kg.

In 2003, the first clinical study done with plerixafor exhibited safety in human volunteers.[56] The combination of plerixafor and G-CSF allows the collection of large numbers of stem cells in few apheresis sessions and can salvage those who fail G-CSF mobilization alone and has been approved by food and drug administration in patients having non-Hodgkin's lymphoma and multiple myeloma.[57-59]

Significant increase in circulating CD34+ cells were observed, when plerixafor was administered after 4 to 5 days of G-CSF. However long term follow up is needed to evaluate safety of Plerixafor mobilized stem cell autograft.[60] Plerixafor has also been used with pediatric patients as mobilizing regimen.[61]

Other agents which are investigated as chemokine are parathyroid hormone, VLA-4 antibodies, retinoic acid receptors, Gro-β, IL-8, CXCR4 peptide etc.[62-69] Initial studies have demonstrated efficacy of these molecules in mobilization of HSCs and progenitor cells; however, their clinical application yet to be explored.

Factors which affect stem cell mobilization include age, low platelet counts, prior radiotherapy, and disease conditions such as Hodgkin's lymphoma. The mobilization capacity of patients having hematologic malignancies is lower in comparison to patients having solid tumors.

Factors which affect PBSCs yield are chemotherapy dosage, cytokine dosage, and combinations of cytokines or with chemotherapy.[70]

Collection- apheresis technique

For PBSCs collection, various apheresis devices have been approved by FDA. PBSCs collection is performed by single or multiple continuous flow apheresis technique. Acid citrate dextrose is commonly used as anticoagulant. Stem cells are collected either in standard low volume or in large volume. Lower volume procedure typically involves processing volume of 10-15L i.e. two-three times the patient's blood volume. Large volume leukopheresis are defined as the processing of greater than three volumes of blood at one session. Large volume leukapheresis results in higher CD34+ cells yield per apheresis session; however patient discomfort and citrate toxicity are associated concerns.[71-75] Collection normally starts when CD34+ cells reach to a level of 5-20 CD34+ cells/µl. Apheresis procedures are normally safe; though common complications associated with apheresis method are citrate toxicity, thrombocytopenia, hypovolemia, catheter malfunction, microbial infection etc.

Expansion of Peripheral blood stem cells

In many patients even after several collections, the numbers of mobilized cells do not achieve therapeutic doses and some patients do not proceed after analyzing the cost of pre and post apheresis implications. To address these issues, researchers are trying to find ways to expand these cells ex-vivo. The criteria need to be fulfilled, when considering the in vitro expansion of peripheral blood stem cells.[76]

- They must be able to expand on larger scale without losing their self-renewal ability.
- Expansion method should be safe for transplanting these cells; should be free from feeder layers, microbial agents.

Various studies have explored expansion of HSCs ex-vivo, which include the use of cytokine cocktail, copper chelators, signaling molecule, transcription factors. The incorporation of Interleukins IL-1, IL-3, IL-6, G-CSF and SCF to culture has demonstrated 50-fold increases in CD34+ expansion.

Variables which affect the expansion of stem cell ex - vivo:

- Combination of cytokines used
- Inclusion/ exclusion of serum containing media
- Cytokine concentration
- Initial cell density
- Culture duration
- Static or dynamic system used

Table 2: Clinical studies done with ex-vivo expanded PBSC.

Author	Culture conditions	Study
Brugger et al	Medium-RPMI with 2% auto plasma, Cytokine-SCF, IL-1b, IL-3, IL-6, EPO	Ten patients were given transplants of autologous progenitor cells that had been generated ex-vivo. No toxic effects were observed with the infusion of the generated cells. The cells promoted a rapid and sustained hematopoietic recovery. The pattern of hematopoietic reconstitution was identical to that in historical controls treated with unseparated mononuclear cells. [77]
Williams et al	X-Vivo10, 1% HAS PIXY 321	The ex-vivo cultured PBPC's in gas permeable bags were transplanted in nine patients with metastatic breast cancer. 8 Patients demonstrated absolute neutrophil counts >500/pL on a median of 8 days and platelet counts >50,000/pL were achieved by day 12 for the seven patients.[78]
Alcorn et al	Autoserum, Cytokine- SCF, IL-1b, IL-3, IL-6, EPO	Ex-vivo expanded peripheral blood progenitor cells were transplanted to 10 patients with non-myeloid malignancy. No adverse effects were observed. No differences in either neutrophil or platelet recovery between the patients who received expanded cells and historical controls.[79]
Mcniece et al	Amgen defined media Cytokine SCF, G-CSF, MGDF	PBPCs from patients with breast cancer were cultured for 10 days in Teflon bags. No graft failure observed. Patients engrafted neutrophils in a median of 6 days.[80]

Table 3: Peripheral blood stem cell transplantation in Myeloma patients.

Author	Mobilizing agent	Results
Tricot et al	Chemotherapy (cyclophosphamide) followed by G-CSF at a dose of 5µg/kg/d and GM-CSF 250µg/m^2	The threshold dose of CD 34 cells for prompt engraftment was 2.0 x 10^6/kg, whereas greater than 5 x 10^6/kg CD34 cells were required to have rapid recovery. Rapid platelet recovery was invariably observed within 14 days when greater than 5 x10^6/kg CD34 cells were infused, irrespective of the duration of prior therapy. [81]
Tribalto M et al	Cyclophosphamide chemotherapy	75% of patients responded with complete remission rate of 31%. Study confirms feasibility of transplantation in multiple myeloma patients. [82]
Steidl U et al	Cyclophosphamide and polyethylene glycol conjugated G-CSF or G-CSF	Pegfilgrastim after chemotherapy demonstrated capability of mobilizing a sufficient number of $CD34^+$ cells for successful auto transplantation with early engraftment and sustained hematological reconstitution in patients with myeloma.[83]
Alegre A et al	Chemotherapy alone or combined with G-CSF or GM-CSF	Very low toxicity was observed. Autologus PBSC transplanatation is feasible option in myeloma patients.[84]

Clinical efficacy of ex-vivo expanded peripheral blood progenitor cells have been studied by different researchers that have been summarized in Table 2. Challenges with ex-vivo expanded HSC are homing and survival of transplanted cells, and retention of multi-lineage differentiation potential.

THERAPEUTIC APPLICATIONS

Multiple myeloma

Over the last decade therapeutic modalities for multiple myeloma have changed significantly. Hematopoietic cell transplantation has shown superiority over chemotherapy in terms of disease free and overall survival. Some studies performed with PBSCs transplantation in treating multiple myeloma has been summarized in Table 3.

Leukemia

Hematopoietic stem cells especially PBSCs transplantation has been used extensively in Acute and Chronic leukemia patients. Table-4 summarizes some studies performed with PBSCs transplant in treating leukemia.

Other diseases

PBSC's transplantation has been also tried in patients suffering from Multiple Sclerosis, Aplastic Anemia, Diabetic foot, Thalassemia etc. Clinical studies done with various diseases with PBSCs transplantation have been summarized in Table 5.

Table 4: Peripheral blood stem cell transplantation in leukemia patients

Author	Conditioning therapy	Study
Schmitz N et al	Standard dose of cyclophosphamide, melphalan, or etoposide and filgrastim	Neutrophil and platelet recovery were significantly faster after transplantation of peripheral blood stem cells in comparison to bone marrow transplant. Acute and chronic graft versus host disease was higher in PBSC transplant. To exactly determine advantage of both cells, long term studies are necessary.[85]
Matsubara et al	Subcutaneous injection of G-CSF (10µg/kg/day) for 5 days	None of patients developed acute graft versus host disease. The granulocyte and platelet count were $0.5x10^9$/l and $20*10^9$/l by 16 and 21 days respectively. Allogenic PBSCT was found safe procedure in pediatric patients. [86]
Visani G et al	G-CSF mobilization after high dose cytarabine consolidation (Novia)	The neutrophil and platelet recovery time were shorter for PBSC group. No significant toxicity was observed; faster recovery occurred and reduced need for transfusion support. [87]

Table 5: Clinical application of Peripheral Blood Stem cell in different diseases.

Diseases	Author	Conditioning therapy	Results
Multiple Sclerosis	Fassas A et al	Cyclophosphamide (4 g/m2) and G/GM- CSF (5µg/kg/day)	Autologus stem cell transplant was found feasible in MS. No toxic signs were observed. Neurological improvements have been detected.[88]
Diabetic foot gangrene	Xu et al	Subcutaneous injection of 5µg/kg/day G-CSF or Filgrastim 10µg/kg/day twice in day	Recombinant human G-CSF mobilized peripheral blood stem cell transplantation effectively increased the blood supply of the lower extremities in patients with diabetic foot.[89]
Aplastic anemia	Maschan et al	Cyclophosphamide 50 mg/kg on day's -5 to-2 and Antithymocyte globulin 30 mg/kg on days -3 to -1. G-CSF 10 µg/kg bw day for 5 days	Granulocyte engraftment was achieved on day 18 and platelet engraftment by day 40. After rituximab administration at day 118, reticulocytes rose to 5.7% by day 132.[90]
Aplastic anemia	Mishra PC et al	Fludarabine from day -10 to day -5, cyclophosphamide 60 mg/kg/day from day -6 to -5 and antithymocyte globulin 30 mg/kg/day from day -4 to -1	The outcome and survival rate were comparable to those achieved with historical bone marrow transplant data. Acute GvHD was seen in 25% patients, Chronic GvHD was seen in 32% of cases. These were mostly associated with dry skin and changes in pigmentation, which subsided over time. PBSCT was found safe in aplastic anemia patients whose transplant has been delayed. [91]
Myocardial infarction	Kang et al	Subcutaneous injections of G-CSF at 10 mg/kg body weight for 3 consecutive days.	PBSC therapy with G-CSF improved the left ventricular systolic function in myocardial infarction patients, which maintained until the 24-month follow-up. During the 5-year follow-up, stem cell infusion was associated with significantly reduced cardiovascular events, even in diabetic patients.[92]
Thalassemia	Yesilipek et al	Busulphan (BU) 16 mg/kg and cyclophosphamide (CY) 200 mg/kg G-CSF as mobilizer for 5 days 5µg/kg	Fifteen patients with beta-thalassemia received an allogeneic peripheral blood stem cell transplant. No patients exhibited engraftment failure or recurrence of thalassemia. The neutrophil and platelet engraftment times were day 12 and day 16, respectively. The survival percentage was 86.6%. [93]

CONCLUSION

Stem cell has recently gained importance in clinical applications due to their self-renewal and multilineage differentiation potential. Peripheral blood stem cell transplantation in treating various malignancies related to hematological conditions has recently showed a greater alternative to conventional bone marrow transplant. The PBSCs are collected from peripheral circulation, when

mobilized with growth factors. G-CSF or pegfilgrastim alone or in combination with chemotherapy are commonly used mobilizing agents for PBSCs mobilization. Current research is focused on the development of novel hematopoietic growth factors to have better peripheral stem cells yield and as well reduce the treatment cost. PBSCs transplantation can be potential therapeutic option for treatment of hematologic malignancies with the further developments in cytokine research and ex-vivo expansion technology.

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REFERENCES

1. Korbling M, Freireich EJ. Twenty-five years of peripheral blood stem cell transplantation. Blood. 2011;117(24):6411-6.
2. Powles R, Mehta J, Kulkarni S, Treleaven J, Millar B, Marsden J, et al. Allogeneic blood and bone-marrow stem-cell transplantation in haematological malignant diseases: a randomized trial. Lancet. 2000;355(9211):1231-7.
3. Chang YJ, Weng CL, Sun LX, Zhao YT. Allogenic 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. 2012;91(3):427-37.
4. Zhang H, Chen J, Que W. Allogeneic peripheral blood stem cell and bone marrow transplantation for hematologic malignancies: meta-analysis of randomized controlled trials. Leuk Res. 2012;36(4):431-7.
5. Bensinger WI, Martin PJ, Storer B, Clift R, Forman SJ, Negrin R, et al. Transplantation of bone marrow compared with peripheral- blood cells from HLA-identical relatives in patients with hematologic cancers. N Engl J Med. 2001;344(3):175-81.
6. Champlin RE, Schmitz N, Horwitz MM, Chapuis B, Chopra R, Cornelissen JJ, et al. Blood stem cells compared with bone marrow as a source of hematopoietic cells for allogeneic transplantation. IBMTR histocompatibility and stem cell sources working committee and the European group for blood and marrow transplantation (EBMT). Blood. 2000;95(12):3702-9.
7. Bensinger WI. Allogeneic transplantation: Peripheral blood versus bone marrow. Curr Opin Oncol. 2012;24(2):191-6.
8. Ringden O, Labopin M, Bacigalupo A, Arcese W, Schaefer UW, Willemze R, et al. 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. 2002;20(24):4655-64.
9. Korbling M, Anderlini P. Peripheral blood stem cell versus bone marrow allotransplantation: does the source of hematopoietic stem cell matter? Blood. 2001;98(10):2900-8.
10. Meisel R, Klingebiel T, Dilloo D. Peripheral blood stem cell versus bone marrow in pediatric unrelated donor stem cell transplantation. Blood. 2013;121(5):863-5.
11. Kotasek D, Shepherd KM, Sage RE, Dale BM, Norman JE, Charles P, et al. Factors affecting blood stem cell collections following high-dose cyclophosphamide mobilization in lymphoma, myeloma and solid tumors. Bone Marrow Transplant. 1992;9(1):11-7.
12. Mollee P, Pereira D, Nagy T, Song K, Saragosa R, Keating A, et al. Cyclophosphamide, etoposide, and G-CSF to mobilize peripheral blood stem cells for autologous stem cell transplantation in patients with lymphoma. Bone Marrow Transplant. 2002;30(5):273-8.
13. Pavone V, Gaudio F, Guarini A, Perrone T, Zonno A, Curci P, et al. Mobilization of peripheral blood stem cells with high dose cyclophosphamide or the DHAP-regimen plus G-CSF in non-hodgkin's lymphoma. Bone Marrow Transplant. 2002;29(4):285-90.
14. Juttner CA, To LB, Ho JQ, Bardy PG, Dyson PG, Haylock DN, et al. Early lympho-hemopoietic recovery after autografting using peripheral blood stem cells in acute non-lymphoblastic leukemia. Transplant Proc. 1988;20(1):40-2.
15. Reiffers J, Bernard P, David B, Vezon G, Sarrat A, Marit G, et al. Successful autologous transplantation with peripheral blood hemopoietic cells in a patient with acute leukemia. Exp Hematol. 1986;14(4):312–5.
16. Nervi B, Link DC, DiPersio JF. Cytokines and hematopoietic stem cell mobilization. J Cell Biochem. 2006;99(3):690-705.
17. Ringden O, Remberger M, Runde V, Bornhauser M, Blau IW, Basara N, et al. Faster engraftment of neutrophils and platelets with peripheral blood stem cells from unrelated donors: a comparison with marrow transplantation. Bone Marrow Transplant. 2000;25(Suppl 2):S6-S8.
18. Bensinger W, Singer J, Applebaum F, Lilleby K, Longin K, Rowley S, et al. Autologus transplantation with peripheral blood with mononuclear cells collected after administration of recombinant granulocyte stimulating factor. Blood. 1993;81(11):3158-63.
19. Koenigsmann M, Jentsch-Ullrich K, Mohren M, Becker E, Heim M, Franke A. The role of diagnosis in patients failing peripheral blood progenitor cell mobilization. Transfusion. 2004;44(5):777–84.
20. Carral A, de la RJ, Martin G, Molla S, Martinez J, Sanz GF, et al. Factors influencing the collection of peripheral blood stem cells in patients with acute myeloblastic leukemia and nonmyeloid malignancies. Leuk Res. 2003;27(1):5-12.

21. Holm M. Not all healthy donors mobilize hematopoietic progenitor cells sufficiently after G-CSF administration to allow for subsequent CD34 purification of the leukapheresis product. J Hematother. 1998;7(2):111-3.
22. Sloand EM, Read EJ, Scheinberg P, Tang Y, More K, Leitman SF, et al. Mobilization, collection, and immunomagnetic selection of peripheral blood CD34 cells in recovered aplastic anemia patients. Transfusion. 2007;47(7):1250-3.
23. Falzetti F, Aversa F, Minelli O, Tabilio A. Spontaneous rupture of spleen during peripheral blood stem cell mobilization in a healthy donor. Lancet. 1999;353:555.
24. Balaguer H, Galmes A, Ventayol G, Bargay J, Besalduch J. Splenic rupture after granulocyte-colony-stimulating factor mobilization in peripheral blood progenitor cell donor. Transfusion. 2004;44(8):1260-1.
25. Bakanay SM, Demirer T. Novel agents and approaches for stem cell mobilization in normal donors and patients. Bone Marrow Transplant. 2012;47(9):1154-63.
26. Lemoli RM, D'addio A. Hematopoietic stem cell mobilization. Haematol. 2008; 93(3):321-4.
27. Gazitt Y. Comparison between granulocyte-colony stimulating factor and granulocyte-macrophage colony stimulating factor in the mobilization of peripheral blood stem cells. Curr Opin Hematol. 2002;9(3):190-8.
28. Koc ON, Gerson SL, Cooper BW, Laughlin M, Meyerson H, Kutteh L, et al. Randomized cross-over trial of progenitor-cell mobilization: high-dose cyclophosphamide plus granulocyte colony-stimulating factor (G-CSF) versus granulocte-macrophage colony-stimulating factor plus G-CSF. J Clin Oncol. 2000;18(9):1824-30.
29. Devine SM, Brown RA, Mathews V, Trinkaus K, Khoury H, Adkins D, et al. Reduced risk of acute GVHD following mobilization of HLA-identical sibling donors with GM-CSF alone. Bone Marrow Transplant. 2005;36(6):531-8.
30. Vasu C, Dogan RN, Holterman MJ, Prabhakar BS. Selective induction of dendritic cells using granulocyte macrophage-colony stimulating factor, but not fms-like tyrosine kinase receptor 3-ligand, activates thyroglobulin-specific CD4+/CD25+ T cells and suppresses experimental autoimmune thyroiditis. J Immunol. 2003;170(11):5511-22.
31. Parajuli P, Mosley RL, Pisarev V, Chavez J, Ulrich A, Varney M, et al. Flt3 ligand and granulocyte-macrophage colony-stimulating factor preferentially expand and stimulate different dendritic and T-cell subsets. Exp Hematol. 2001;29(10):1185-93.
32. Olivieri A, Offidani M, Cantori I, Ciniero L, Ombrosi L, Masia MC, et al. Addition of erythropoietin to granulocyte colony-stimulating factor after priming chemotherapy enhances hemopoietic progenitor mobilization. Bone marrow Transplant. 1995;16(6):765-70.
33. Perillo A, Ferrandina G, Pierelli L, Rutella S, Mancuso S, Scambia G. Cytokines alone for PBPC collection in patients with advanced gynaecological malignancies: G-CSF vs G-CSF plus EPO. Bone Marrow Transplant. 2004;34(8):743-4.
34. Waller CF, von Lintig F, Daskalakis A, Musahi V, Lange W. Mobilization of peripheral blood progenitor cells in patients with breast cancer: a prospective randomized trial comparing rhG-CSF with the combination of rhG-CSF plus rhEpo after VIP-E chemotherapy. Bone Marrow Transplant 1999;24(1):19-24.
35. Labonte L, Iqbal T, McDiarmid S, Bence-Bruckler I, Huebsch L, Allan D. Continuing erythropoietin during peripheral blood stem cell collection in myeloma: can it reduce toxicity of autologous transplants? Biol Blood Marrow Transplant. 2008;14(1):132-3.
36. Hart C, Grassinger J, Andressen R, Hennemann B. EPO in combination with G-CSF improves mobilization effectiveness after chemotherapy with ifosfamide, epirubicin and etoposide and reduces costs during mobilization and transplantation of autologous hematopoietic progenitor cells. Bone Marrow Transplant. 2009;43(3):197-206.
37. Dawson MA, Schwarer AP, Muirhead JL, Bailey MJ, Bollard GM, Spencer A. Successful mobilization of peripheral blood stem cells using recombinant human stem cell factor in heavily pretreated patients who have failed a previous attempt with a granulocyte-colony-stimulating factor-based regimen. Bone Marrow Transplant. 2005;36(5):389-96.
38. Glaspy JA, Shpall EJ, LeMaistre CF, Briddell RA, Menchaca DM, Turner SA, et al. Peripheral blood progenitor cell mobilization using stem cell factor in combination with filgrastim in breast cancer patients. Blood. 1997;90(8):2939-51.
39. Weaver A, Chang J, Wrigley E, de Wynter E, Woll PJ, Lind M, et al. Randomized comparison of progenitor-cell mobilization using chemotherapy, stem-cell factor, and filgrastim or chemotherapy plus filgrastim alone in patients with ovarian cancer. J Clin Oncol. 1998;16(8):2601-12.
40. Facon T, Harousseau JL, Maloisel F, Attal M, Odriozola J, Alegre A, et al. Stem cell factor in combination with filgrastim after chemotherapy improves peripheral blood progenitor cell yield and reduces apheresis requirements in multiple myeloma patients: a randomized, controlled trial. Blood. 1999;94(4):1218-25.
41. Shpall EJ, Wheeter CA, Turner SA, Yanovich S, Brown RA, Pecora AL, et al. A randomized phase 3 study of peripheral blood progenitor cell mobilization with stem cell factor and filgrastim in high risk breast cancer patients. Blood. 1999;93(8):2491-501.
42. Herbert KE, Morgan S, Prince HM, Westerman DA, Wolf MM, Carney DA, et al. Stem cell factor and high-dose twice daily filgrastim is an effective

strategy for peripheral blood stem cell mobilization in patients with indolent lymphoproliferative disorders previously treated with fludarabine: results of a phase II study with an historical comparator. Leukemia. 2009;23(2):305-12.
43. Stiff P, Gingrich R, Luger S, Wyres MR, Brown RA, Lemaistre CF, et al. A randomized phase 2 study of PBPC mobilization by stem cell factor and filgrastim in heavily pretreated patients with Hodgkin's disease or non-Hodgkin's lymphoma. Bone Marrow Transplant. 2000;26(5):471-81.
44. Murray LJ, Luens KM, Estrada MF, Bruno E, Hoffman R, Cohen RL, et al. Thrombopoietin mobilizes CD34+ cell subsets into peripheral blood and expands multilineage progenitors in bone marrow of cancer patients with normal hematopoiesis. Exp Hematol. 1998;26(3):207-16.
45. Somlo G, Sniecinski I, ter Veer A, Longmate J, Knutson G, Vuk-Pavlovic S, et al. Recombinant human thrombopoietin in combination with granulocyte colony-stimulating factor enhances mobilization of peripheral blood platelet concentration, and accelerates hematopoietic recovery following high-dose chemotherapy. Blood. 1999;93(9):2798-806.
46. Linker C, Anderlini P, Herzig R, Christiansen N, Somlo G, Bensinger W, et al. Recombinant human thrombopoietin augments mobilization of peripheral blood progenitor cells for autologous transplanatation. Biol Blood Marrow Transplant. 2003;9(6):405-13.
47. Gajewski JL, Rondon G, Donato ML, Anderlini P, Korbling M, Ippoliti C, et al. Use of thrombopoietin in combination with chemotherapy and granulocyte colony-stimulating factor for peripheral blood progenitor cell mobilization. Biol Blood Marrow Transplant. 2002;8(10):550-6.
48. Steidl U, Fenk R, Bruns I, Neumann F, Kondakci M, Hoyer B, et al. Successful transplantation of peripheral blood stem cells mobilized by chemotherapy and a single dose of pegylated G-CSF in patients with multiple myeloma. Bone Marrow Transplant. 2005;35(1):33-6.
49. Fruehauf S, Klaus J, Huesing J, Veldwijk MR, Buss EC, Topaly J, et al. Efficient mobilization of peripheral blood stem cells following CAD chemotherapy and a single dose of pegylated G-CSF in patients with multiple myeloma. Bone Marrow Transplant. 2007;39:743-50.
50. Isidori A, Tani M, Bonifazi F, Zinzani P, Curti A, Motta MR, et al. Phase II study of a single pegfilgrastim injection as an adjunct to chemotherapy to mobilize stem cells into the peripheral blood of pretreated lymphoma patients. Haematol. 2005;90(2):225-31.
51. Putkonen M, Rauhala A, Pelliniemi TT, Remes K. Single dose pegfilgrastim is comparable to daily filgrastim in mobilizing peripheral blood stem cells: a case-matched study in patients with lymphoproliferative malignancies. Ann Hematol. 2009;88(7):673-80.
52. Simona B, Cristina R, Luca N, Sara S, Aleksandra B, Paola B, et al. A single dose of pegfilgrastim versus daily filgrastim to evaluate the mobilization and the engraftment of autologous peripheral hematopoirtic progenitors in malignant lymphoma patients candidate for high-dose chemotherapy. Transfus Apher Sci. 2010;43(3):321-6.
53. Hosing C, Qazilbash MH, Kebriaei P, Giralt S, Davis MS, Popat U, et al. Fixed-dose single agent pegfilgrastim for peripheral blood progenitor cell mobilization in patients with multiple myeloma. Br J Haematol. 2006;133(5):533-7.
54. Kroschinsky F, Holig K, Poppe-Thiede K, Zimmer K, Ordemann R, Blechschmidt M, et al. Single-dose pegfilgrastim for the mobilization of allogeneic CD34+ peripheral blood progenitor cells in healthy family and unrelated donors. Haematol. 2005;90(12):1665-71.
55. Mohty M, Duarte RF, Croockewit S, Hubel K, Kvalheim G, Russell N. The role of plerixafor in optimizing peripheral blood stem cell mobilization for autologous stem cell transplantation. Leukemia. 2011;25(1):1-6.
56. Liles WC, Broxmeyer HE, Rodger E, Wood B, Hubel K, Cooper S, et al. Mobilization of hematopoietic progenitor cells in healthy volunteers by AMD3100, a CXCR4antagonist. Blood. 2003;102(8):2728-30.
57. Liles WC, Rodger E, Broxmeyer HE, Dehner C, Badel K, Calandra G, et al. Augmented mobilization and collection of CD34+ hematopoietic cells from normal human volunteers stimulated with granulocyte-colony-stimulating factor by single-dose administration of AMD3100, a CXCR4 anatogonist. Transfusion. 2005;45(3):295-300.
58. DiPersio JF, Stadtmauer EA, Nademanee A, Micallef INM, Stiff PJ, Kaufman JL, et al. Plerixafor and G-CSF versus placebo and G-CSF to mobilize hematopoietic stem cells for autologous stem cell transplantation in patients with multiple myeloma. Blood. 2009;113(23):5720-6.
59. Dipersio JF, Micallef IN, Stiff PJ, Bolwell BJ, Maziarz RT, Jacobsen E, et al. Phase III prospective randomized double-blind placebo-controlled trial of plerixafor plus granulocyte-colony-stimulating factor compared with placebo plus granulocyte colony-stimulating factor for autologous stem cell mobilization and transplantation for patients with non-Hodgkin's lymphoma. J Clin Oncol 2009;27(28):4767-73.
60. Jantunen E, Varmavuo V. Plerixafor for mobilization of blood stem cells in autologous transplanatation: an update. Expert Opin Biol Ther. 2014;14(6):851-61.
61. Gardellini A, Babic A, Gigli F, Liptrott SJ, Martinelli G, Laszlo D. Successful mobilization of peripheral blood stem cells in children using

plerixafor: a case report and review of the literature. Blood Transfusion. 2013;11(2):308-10.
62. Brunner S, Zaruba MM, Huber B, David RM, Vallaster M, Assmann G, et al. Parathyroid hormone effectively induces mobilization of progenitor cells without depletion of bone marrow. Exp Hematol. 2008;36(9):1157-66.
63. Ballen KK, Shpall EJ, Avigan D, Yeap BY, Fisher DC, McDermott K, et al. Phase I trial of parathyroid hormone to facilitate stem cell mobilization. Biol Blood Marrow Transplant. 2007;13(7):838-43.
64. Zohren F, Toutzaris D, Klarner V, Hartung HP, Kieseier B, Haas R. The monoclonal anti-VLA-4 antibody natalizumab mobilizes CD34+ hematopoietic progenitor cells in humans. Blood. 2008;111(7):3893-5.
65. Carlo-Stella C, Di Nicola M, Milani R, Guidetti A, Magni M, Milanesi M, et al. Use of recombinant human growth hormone (rhGH) plus recombinant human granulocyte colony-stimulating factor (rhG-CSF) for the mobilization and collection of CD34+ cells in poor mobilizers. Blood. 2004;103(9):3287-95
66. Herbert KE, True S, McArthur G, Prince HM. Safety and efficacy of combining ATRA with G-CSF in HSPC mobilization; a pilot study in multiple myeloma and non-Hodgkin's lymphoma patients. Bone Marrow Transplant. 2007;40(8):801-3.
67. Pelus LM, Bian H, Fukuda S, Wang D, Merzouk A, Salari H. The CXCR4 agonist peptide CTCE-0021 rapidly mobilise polymorphonuclear neutrophils and hematopoietic progenitor cells into peripheral blood and synergizes with granulocyte colony-stimulating factor. Exp Hematol. 2005;33(3):295-307.
68. Abraham M, Biyder K, Begin M, Wald H, Weiss ID, Galun E, et al. Enhanced unique pattern of hematopoietic cell mobilization induced by the CXCR4 antagonist 4F-benzoyl-TN14003. Stem Cells. 2007;25:2158-66.
69. Fukuda S, Bian H, King AG, Pelus LM. The chemokine GRO β mobilizes early hematopoietic stem cells characterized by enhanced homing and engraftment. Blood. 2007;110(3):860-9.
70. Lie AK, L Bik To. Peripheral blood stem cells: transplantation and beyond. Oncol. 1997;2(1):40-9.
71. Sevilla J, Gonzalez-vicent M, Madero L, Garcia-Sanchez F, Diaz MA. Large volume leukapheresis in small children: safety profiles and variable affecting peripheral blood progenitor cell collection. Bone Marrow Transplant 2003;31(4):263-7.
72. Cecyn KZ, Seber A, Ginani VC, Goncalves AV, Carom EM, Oguro T, et al. Large-volume leukapheresis for peripheral bold progenitor cell collection in low body weight pediatric patients: a single center experience. Transfus Apher Sci. 2005;32(3):269-74.
73. Bojanic I, Dubravcic K, Batinic D, Cepulic BG, Mazic S, Hren D, et al. Large volume leukapheresis: Efficacy and safety of processing patient's total blood volume six times. Transfus Apher Sci. 2011;44(2):139-47.
74. Gasova Z, Marinov I, Vodvarkova S, Bohmova M, Bhuyian-ludvikova Z. PBPC collection techniques: standard versus large volume leukapheresis (LVL) in donors and in patents. Transfus Apher Sci. 2005;32(2):167-76.
75. Abrahamsen JF, Stamnesfet S, Liseth K, Hervig T, Bruserud O. Large volume leukapheresis yield more viable CD34+ cells and colony-forming units than normal volume leukapheresis, especially in patients who mobilize low numbers of CD34+ cells. Transfusion. 2005;45(2):248-53.
76. Devine SM, Lazarus HM, Emerson SG. Clinical application of hematopoetic progenitor cells expansion: current status and future prospects. Bone Marrow Transplant. 2003; 31(4):241-52.
77. Brugger W, Heimfeld S, Berenson RJ, Mertelsmann R, Kanz L. Reconstitution of hematopoiesis after high dose chemotherapy by autologous progenitor cells generated ex vivo. N Engl J Med. 2001;333(5):283-7.
78. Williams SF, Lee WJ, Bender JG, Zimmerman T, Swinney P, Blake M, et al. Selection and expansion of peripheral blood CD34+ cells in autologous stem cell transplantation for breast cancer. Blood. 1996;87(5):1687-91.
79. Alcorn MJ, Holyoake TL, Richmond L, Pearson C, Farrell E, Kyle B, et al. CD 34-positice cells isolated from cryopreserved peripheral-blood progenitor cells can be expanded ex vivo and used for transplantation with little or no toxicity. J Clin Oncol. 1996;14(6):1839-47.
80. Mcniece I, Jones R, Bearman SI, Cagnoni P, Nieto Y, Franklin W, et al. Ex vivo expanded peripheral blood progenitor cells provide rapid neutrophil recovery after high-dose chemotherapy in patients with breast cancer. Blood. 2000;96(9):3001-7.
81. Tricot G, Jagannath S, Vesole D, Nelson J, Tindle S, Langdon M, et al. Peripheral Blood stem cell transplants for multiple myeloma: Identification of favorable variables for rapid engraftment in 225 patients. Blood. 1995;85(2):588-96.
82. Tribalto M, Amadori S, Cudillo L, Caravita T, Poeta GD, Meloni G, et al. Autologus peripheral blood stem cell transplantation as first line treatment of multiple myeloma: an Italian multicenter study. Haematol. 2000;85(1):52-8.
83. Steidl U, Fenk R, Bruns I, Neumann F, Kondakci M, Hoyer B, et al. Successful transplantation of peripheral blood stem cells mobilized by chemotherapy and single dose of pegylated G-CSF in patients with multiple myeloma. Bone Marrow Transplant 2005;35(1):33-6.
84. Alegre A, Diaz-mediavill J, San-miguel J, Martinez R, Larana JG, Sureda, A et al. Autologus peripheral blood stem cell transplantation for multiple myeloma: a report of 259 cases from the Spanish registry. Bone Marrow Transplant. 1998;21(2):133-40.

85. Schmitz N, Beksac M, Bacigalupo A, Ruutu A, Nagler A, Gluckman E, et al. Filgrastim-mobilized peripheral blood progenitor cells versus bone marrow transplantation for treating leukemia: 3 year results from the EBMT randomized trial. Hematol. 2005;90(5):643-8.
86. Matsubara H, Makimoto A, Takayama J, Higa T, Saito T, Kanda Y, et al. Possible clinical benefits of the use of peripheral blood stem cells over bone marrow in the allogeneic transplantation setting for the treatment of childhood leukemia. Jpn J Clin Oncol. 2001;31(1):31-4.
87. Visani G, Lemoli RM, Tosi P, Martinelli G, Testoni N, Ricci P, et al. Use of peripheral blood stem cells for autologous transplantation in acute myeloid leukemia patients allows faster engraftment and equivalent-disease free survival compared with bone marrow cells. Bone Marrow Transplant. 1999;24(5):467-72.
88. Fassas A, Anagnostopoulos A, Kazis A, Kapinas K, Sakellari I, Kimiskidis V, et al. Peripheral blood stem cell transplantation in the treatment of progressive multiple sclerosis: first result of a pilot study. Bone Marrow Transplant. 1997;20(8):631-8.
89. Xu S, Liang T. Clinical observation of the application of autologous peripheral blood stem cell transplantation for the treatment of diabetic foot gangrene. Exp Ther Med. 2016;11(1):283-8.
90. Maschan AA, Skorobogatova EV, Balashov DN, Pashanov ED, Trakhtman PE, Schipitzina IP, et al. Successful treatment of pure red cell aplasia with a single dose of rituximab in a child after major ABO incompatible peripheral blood allogeneic stem cell transplantation for acquired aplastic anemia. Bone Marrow Transplant. 2002;30(6):405-7.
91. Mishra PC, Seth T, Mahapatra M. Peripheral blood stem cell transplant in aplastic anemia. Biol Blood Marrow Transplant. 2015;21(2):S38.
92. Kang H, Kim M, Lee H, Park K, Lee W, Cho YS, et al. Five year results of intra coronary infusion of the mobilized peripheral blood stem cells by granulocyte-colony stimulating factor in patients with myocardial infarction. Eur Heart J. 2012;33(24):3062-9.
93. Yesilipek MA, Hazar V, Kupesiz A, Kizilors A, Uguz A, Yegin O. Peripheral blood stem cell transplantation in children with beta thalassemia. Bone Marrow Transplant. 2001;28(11):1037-40.

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