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

**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.](image)

- 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 allogeneic 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 hemological 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. 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.

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. Plerixafor has also been used with pediatric patients as mobilizing regimen. Other agents which are investigated as chemokine are parathyroid hormone, VLA-4 antibodies, retinoic acid receptors, Gro-β, IL-8, CXCR4 peptide etc. 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.

**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 leukapheresis 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. 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.

- 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
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.

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Culture conditions</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brugger et al</td>
<td>Medium-RPMI with 2% auto plasma, Cytokine-SCF, IL-1b, IL-3, IL-6, EPO</td>
<td>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.</td>
</tr>
<tr>
<td>Williams et al</td>
<td>X-Vivo10, 1% HAS PIXY 321</td>
<td>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 &gt;500/pL on a median of 8 days and platelet counts &gt;50,000/pL were achieved by day 12 for the seven patients.</td>
</tr>
<tr>
<td>Alcorn et al</td>
<td>Autoserum, Cytokine- SCF, IL-1b, IL-3, IL-6, EPO</td>
<td>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.</td>
</tr>
<tr>
<td>Mcniece et al</td>
<td>Amgen defined media Cytokine SCF, G-CSF, MGDF</td>
<td>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.</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Mobilizing agent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricot et al</td>
<td>Chemotherapy (cyclophosphamide) followed by G-CSF at a dose of 5µg/kg/d and GM-CSF 250µg/m²</td>
<td>The threshold dose of CD 34 cells for prompt engraftment was 2.0 x 10⁹/kg, whereas greater than 5 x 10⁹/kg CD34 cells were required to have rapid recovery. Rapid platelet recovery was invariably observed within 14 days when greater than 5 x10⁹/kg CD34 cells were infused, irrespective of the duration of prior therapy.</td>
</tr>
<tr>
<td>Tribalto M et al</td>
<td>Cyclophosphamide chemotherapy</td>
<td>75% of patients responded with complete remission rate of 31%. Study confirms feasibility of transplantation in multiple myeloma patients.</td>
</tr>
<tr>
<td>Steidl U et al</td>
<td>Cyclophosphamide and polyethylene glycol conjugated G-CSF or G-CSF</td>
<td>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.</td>
</tr>
<tr>
<td>Alegre A et al</td>
<td>Chemotherapy alone or combined with G-CSF or GM-CSF</td>
<td>Very low toxicity was observed. Autologus PBSC transplanatation is feasible option in myeloma patients.</td>
</tr>
</tbody>
</table>

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Table 4: Peripheral blood stem cell transplantation in leukemia patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Conditioning therapy</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmitz N et al</td>
<td>Standard dose of cyclophosphamide, melphalan, or etoposide and filgrastim</td>
<td>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</td>
</tr>
<tr>
<td>Matsubara et al</td>
<td>Subcutaneous injection of G-CSF (10µg/kg/day) for 5 days</td>
<td>None of patients developed acute graft versus host disease. The granulocyte and platelet count were 0.5x10⁹/l and 20x10⁹/l by 16 and 21 days respectively. Allogenic PBSCT was found safe procedure in pediatric patients.⁸⁶</td>
</tr>
<tr>
<td>Visani G et al</td>
<td>G-CSF mobilization after high dose cytarabine consolidation (Novia)</td>
<td>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</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Author</th>
<th>Conditioning therapy</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Sclerosis</td>
<td>Fassas A et al</td>
<td>Cyclophosphamide (4 g/m²) and G/GM- CSF (5µg/kg/day)</td>
<td>Autologus stem cell transplant was found feasible in MS. No toxic signs were observed. Neurological improvements have been detected.⁸⁸</td>
</tr>
<tr>
<td>Diabetic foot gangrene</td>
<td>Xu et al</td>
<td>Subcutaneous injection of 5µg/kg/day G-CSF or Filgrastim 10µg/kg/day twice in day</td>
<td>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</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>Maschan et al</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>Mishra PC et al</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Kang et al</td>
<td>Subcutaneous injections of G-CSF at 10 mg/kg body weight for 3 consecutive days.</td>
<td>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</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>Yesilipek et al</td>
<td>Busulphan (BU) 16 mg/kg and cyclophosphamide (CY) 200 mg/kg G-CSF as mobilizer for 5 days 5µg/kg</td>
<td>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</td>
</tr>
</tbody>
</table>

**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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Conflict of interest: None declared
Ethical approval: Not Required

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42. Herbert KE, Morgan S, Prince HM, Westermar 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.


