Optimal stem cell source for allogeneic stem cell transplantation for hematological malignancies

Daniel KL Cheuk

Daniel KL Cheuk, Department of Paediatrics and Adolescent Medicine, the University of Hong Kong, Queen Mary Hospital, Hong Kong, China

Author contributions: Cheuk DKL solely contributed to this paper.

Supported by The University of Hong Kong

Correspondence to: Daniel KL Cheuk, FHKAM, Department of Paediatrics and Adolescent Medicine, the University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong, China. cheukkld@hkucc.hku.hk

Telephone: +86-852-22553909 Fax: +86-852-22551523

Received: August 28, 2013 Revised: November 15, 2013 Accepted: December 9, 2013 Published online: December 24, 2013

Abstract

Hematopoietic stem cell transplant (HSCT) is a standard treatment for many hematological malignancies. Three different sources of stem cells, namely bone marrow (BM), peripheral blood stem cells (PBSC) and cord blood (CB) can be used for HSCT, and each has its own advantages and disadvantages. Randomized controlled trials (RCTs) suggest that there is no significant survival advantage of PBSC over BM in Human Leukocyte Antigen-matched sibling transplant for adult patients with hematological malignancies. PBSC transplant probably results in lower risk of relapse and hence better disease-free survival, especially in patients with high risk disease at the expense of higher risks of both severe acute and chronic graft-versus-host disease (GVHD). In the unrelated donor setting, the only RCT available suggests that PBSC and BM result in comparable overall and disease-free survivals in patients with hematological malignancies; and PBSC transplant results in lower risk of graft failure and higher risk of chronic GVHD. High level evidence is not available for CB in comparison to BM or PBSC. The risks and benefits of different sources of stem cells likely change with different conditioning regimen, strategies for prophylaxis and treatment of GVHD and manipulation of grafts. The recent success and rapid advance of double CB transplant and haploidentical BM and PBSC transplants further complicate the selection of stem cell source. Optimal selection requires careful weighing of the risks and benefits of different stem cell source for each individual recipient and donor. Detailed counseling of patient and donor regarding risks and benefits in the specific context of the patient and transplant method is essential for informed decision making.

Key words: Hematopoietic stem cell transplantation; Bone marrow; Peripheral blood stem cell; Cord blood; Hematological malignancy

Core tip: Randomized controlled trials (RCTs) suggest no difference in survival between peripheral blood stem cell (PBSC) and bone marrow (BM) in matched sibling transplant for patients with hematological malignancies. PBSC may result in fewer relapse in high risk patients but more severe graft-versus-host disease (GVHD). For unrelated donor, the only RCT suggests PBSC and BM result in comparable survivals, with PBSC resulting in fewer graft failure but more chronic GVHD. RCT is not available to compare cord blood with BM or PBSC. The risks and benefits of different sources of stem cells likely change with transplant methods and manipulation of grafts.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is now...
Established as a standard therapeutic modality for a variety of malignant and non-malignant diseases. The first successful allogeneic HSCT was done with bone marrow (BM) as the source of hematopoietic stem cells in 1968[6]. In the subsequent 2 decades only bone marrow was used as the source of stem cells for transplantation. In the 1960s, experiments have shown that peripheral blood contains a small number of stem cells[2], which can be enriched by pre-treatment with certain chemotherapeutic drugs and hematopoietic growth factors[3-5]. Therefore mobilized peripheral blood stem cells (PBSC) became another stem cell source for HSCT and PBSC has been increasingly used as it has certain advantages compared with BM. In 1978, cord blood (CB) was found to be a rich source of stem cells[6] and was later successfully used for allogeneic HSCT[7] at a lower cell dose infused compared with BM or PBSC.

Nowadays transplant physicians are faced with 3 viable choices of stem cells for allogeneic HSCT, namely BM, PBSC and CB and clinicians have to face the challenges of selecting the optimal stem cell source. Although all 3 sources of stem cells are capable of reconstituting the hematopoietic system in recipient after transplant, they have many inherent differences in cellular constituents and biological and immunological properties. In this article we shall review the advantages and disadvantages of different sources of stem cells and the available clinical evidence that helps clinicians to make decision.

**Table 1 Comparison of bone marrow, peripheral blood stem cell and cord blood**

|                        | BM                 | PBSC               | CB                     |
|------------------------|--------------------|--------------------|------------------------|
| Typical time frame from initiation of search to transplantation | 3-6 mo             | 3-6 mo             | 2-4 wk                 |
| Usual volume           | 500-2000 mL        | 50-300 mL          | 25-150 mL              |
| Adverse effects for donor | Risks of wound infection, bleeding, general anesthesia, etc. | Risks of bleeding, infection, thrombosis, hypotension, electrolyte disturbance, etc. | No                     |
| Minimal cell dose for transplant | Total nucleated cell: 2 x 10^6/kg | Total CD34+ cell: 2 x 10^6/kg | Total nucleated cell: 2.5 x 10^6/kg |
| Red blood cell content | High               | Low                | Low                    |
| Possibility to give additional stem cell dose | Possible           | Possible           | Impossible             |
| Exposure to dimethyl sulfoxide | No if fresh        | No if fresh        | Yes                    |
| HLA matching requirement | More stringent (7-8 out of 8 matched) | More stringent (7-8 out of 8 matched) | Less stringent (4-6 out of 6 matched) |
| Speed of neutrophil engraftment | About 3 wk         | About 2 wk         | About 4 wk             |
| Speed of immune reconstitution | Faster            | Faster             | Slower                 |
| Risk of graft-versus-host disease | Medium           | Highest            | Lowest                 |
| Risk of post-transplant infections | Lower             | Lower              | Higher                 |
| Risk of latent virus transmission | Higher            | Higher             | Lower                  |
| Possibility of CMV transmission | Higher as most donors are CMV seropositive | Higher as most donors are CMV seropositive | Lower as most CB units do not harbor CMV |
| Risk of relapse for high risk patients | Higher            | Higher             | Higher                 |

PBSC: Peripheral blood stem cell; HLA: Human leukocyte antigen; BM: Bone marrow; CB: Cord blood; CMV: Cytomegalovirus.

Compared with unmanipulated BM, Granulocyte colony stimulating factor-mobilized PBSC and cord blood contain significantly lower amount of red blood cells (RBC) and plasma. This has certain impact on the choice of stem cell source when there is mismatch in blood group between the donor and the recipient, as harvested donor BM must be processed to deplete RBC or plasma or both before infusion to recipient. However, depletion of RBC or plasma is not required for PBSC or cord blood transplants even when blood group is mismatched, as the relatively low amount of RBC and RBC antibodies present in these products are unlikely to cause significant hemolysis. Another important difference among the sources of stem cell is the amount of mature T cells present. PBSC usually contains a lot more mature T cells compared to BM, which in turn contains more T cells compared to CB, and this partly explains the differences in the risk of graft rejection and graft-versus-host disease (GVHD). Depletion of T cells is associated with increased risk of graft rejection and disease relapse, but lower risk of GVHD. The comparison of the characteristics of the 3 different sources of stem cells is presented in Table 1.

We often have to consider and weigh the relative benefits and risks before decision on the source of stem cells for allogeneic HSCT. The selection of stem cell source is often intertwined with the selection of donor. A suggested algorithm for selection of donor and stem cell source is given in Figure 1. One of the basic considerations for allogeneic HSCT is whether a Human Leukocyte Antigen (HLA)-matched related donor is available. Although current results of unrelated donor transplants of many transplant centres are similar to that of matched related donor transplants, the latter is still considered the first choice for most allogeneic HSCTs, as the donor is readily available for initial donation and subsequent back-up, and might be associated with a lower risk of GVHD.

**Selection Among Different Stem Cell Sources**

Although BM, PBSC and CB all contain hematopoietic stem cells, other constituents present in the harvest products before additional manipulation are quite different.
and transplant-related mortality (TRM). Therefore, if a matched related donor is available, the choice of stem cell source is simpler and often remains BM versus PBSC, as related donor CB is unlikely to be available. The transplant physician has to weigh the risks and benefits to both the donor and the recipient, explain the different procedures and experiences of stem cell collection to the donor and help the donor to make informed choices. Clinical evidence on different outcomes of recipients transplanted with BM or PBSC presented below will form important basis for the selection.

The donor's perspective should be given due consideration. A prospective study on donors' experience of BM or PBSC donation found that before donation, BM donors had lower confusion, fewer concerns, and were more prepared for donation compared with PBSC donors. Shortly after donation, BM donors experienced more physical side effects than PBSC donors. BM donors also reported greater impact on their social activities, but had better psychological status and were more likely to indicate that the donation made their lives more meaningful. However, there were no significant longer-term differences between BM and PBSC donors including recovery time.

In case HLA-matched related donor CB with adequate cell dose is available; we have to find an alternative donor, the choice of which often includes mismatched family donor (including HLA-haploidentical donor), unrelated donor, or unrelated CB. The selection usually depends heavily on the urgency of transplant, HLA matching and cell dose of CB available, and preference and experience of the transplant centre. Unrelated CB and mismatched family donor (BM or PBSC) are usually more readily available compared to unrelated donor and therefore if transplant needs to be done urgently, CB or mismatched family donor is sometimes preferable. If HSCT is not urgently required, unrelated donor BM or PBSC should be given due consideration. Since the requirement for HLA matching is less stringent for unrelated CB compared to BM or PBSC, unrelated CB is preferable to unrelated donor BM or PBSC if no 7-8/8 allele-matched unrelated donor (or 9-10/10 HLA allele matched unrelated donor which may be associated with even lower risks of TRM and GVHD) is available, provided that the CB is at least 4/6 HLA-matched with adequate cell dose. If there is no single CB with sufficient cell dose, use of double CB can be considered. If transplant is not urgently required and both good matched unrelated donor and unrelated CB with adequate cell dose are available, other considerations prevail, including the preference and experience of the transplant centre, the patient's disease status, the speed of engraftment, risks of infections and GVHD, age, gender and location of donor, ABO blood group matching.

Figure 1  Suggested algorithm for selection of donor and source of stem cells for patients with hematological malignancies. Need to consider pros and cons of BM and PBSC in the context of donor preference, risk of relapse, conditioning regimen, graft-versus-host disease prophylaxis, and graft manipulations, etc. PBSC: Peripheral blood stem cell; HSCT: Hematopoietic stem cell transplant; HLA: Human leukocyte antigen; BM: Bone marrow.
| Ref.   | No. of patients | Age of patients (yr) | Underlying diseases | Conditioning | Overall survival (BM vs PBSC) | Disease-free survival (BM vs PBSC) | Relapse (BM vs PBSC) | Transplant-related mortality (BM vs PBSC) | Acute graft-versus-host disease (BM vs PBSC) | Chronic graft-versus-host disease (BM vs PBSC) | Median time of neutrophil engraftment (d) (BM vs PBSC) | Median time of platelet engraftment (d) (BM vs PBSC) |
|--------|-----------------|----------------------|---------------------|--------------|-------------------------------|-----------------------------------|---------------------|------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| [23,20] | 56              | 7-59                 | Acute leukemias, CML, MDS, MM, NHL | Myeloablative | 48% vs 56%<sup>1</sup>, (2000 d) | 50% vs 60%<sup>1</sup>, (2000 d) | NA                  | NA                                      | 23% vs 26%<sup>1</sup>, (grades 2-4) | 61% vs 77%<sup>2</sup>, (extensive cGVHD) | 18 vs 15<sup>a</sup> | 18 vs 12<sup>b</sup> |
| [9]    | 39              | 22-51                | Acute leukemias, CML, CLL, MDS, MM, NHL | Myeloablative | 63% vs 70%<sup>2</sup>, (2 yr) | NA                  | 37% vs 0%<sup>4</sup>, (2 yr) | 32% vs 35%<sup>2</sup>, (grades 1-4) | 58% vs 68%<sup>2</sup>, (grades 1-4) | 40% vs 44%<sup>2</sup>, (All cGVHD) | 23 vs 17.5<sup>d</sup> | 18 vs 11<sup>d</sup> |
| [25]   | 61              | 15-62                | Acute leukemias, CML, MDS, PMF | Bu/Cy        | 73% vs 80%<sup>1</sup>, (4 yr) | 55% vs 80%<sup>1</sup>, (4 yr) | 30% vs 33%<sup>2</sup>, (2 yr) | 10% vs 17%<sup>2</sup>, (grades 2-4) | 10% vs 21%<sup>2</sup>, (grades 2-4) | 27% vs 56%<sup>2</sup>, (All cGVHD) | 23 vs 17<sup>a</sup> | 21 vs 13<sup>d</sup> |
| [10,19] | 101             | Mean 37              | Acute leukemias, CML | Myeloablative | 65% vs 67%<sup>2</sup>, (2 yr) | 66% vs 67%<sup>2</sup>, (2 yr) | 15% vs 6%<sup>2</sup>, (2 yr) | 21% vs 25%<sup>2</sup>, (grades 2-4) | 42% vs 44%<sup>2</sup>, (grades 2-4) | 36% vs 65%<sup>b</sup>, (All cGVHD) | 21 vs 153 | 21 vs 13<sup>d</sup> |
| [15-18] | 329             | 19-58                | Acute leukemias, CML, MDS | Myeloablative | 65% vs 65%<sup>2</sup>, (2 yr) | 60% vs 56%<sup>2</sup>, (3 yr) | 24% vs 20%<sup>2</sup>, (10 yr) | 32% vs 24%<sup>2</sup>, (grades 2-4) | 42% vs 44%<sup>2</sup>, (grades 2-4) | 56% vs 74%<sup>c</sup>, (All cGVHD) | 19% vs 36%<sup>b</sup>, (extensive cGVHD) | 15 vs 12<sup>c</sup> | 20 vs 15<sup>d</sup> |
| [12,13,20] | 172            | 12-55                | Acute leukemias, CML, CLL, MDS, MM, lymphomas | Myeloablative | 54% vs 66%<sup>2</sup>, (2 yr) | 45% vs 65%<sup>2</sup>, (2 yr) | 25% vs 14%<sup>4</sup>, (2 yr) | 30% vs 21%<sup>2</sup>, (grades 2-4) | 57% vs 64%<sup>2</sup>, (grades 2-4) | 52% vs 63%<sup>2</sup>, (All cGVHD) | 21 vs 16<sup>d</sup> | 19 vs 13<sup>d</sup> |
| [11]   | 227             | 19-64                | AML, CML, MDS | Bu/Cy        | 60% vs 66%<sup>1</sup>, (30 mo) | NA                  | 9% vs 9%<sup>2</sup>, (10 yr) | 32% vs 21%<sup>2</sup>, (grades 2-4) | 44% vs 44%<sup>2</sup>, (grades 2-4) | 69% vs 85%<sup>2</sup>, (extensive cGVHD) | 30% vs 40%<sup>2</sup>, (extensive cGVHD) | 23 vs 19<sup>2</sup> | 22 vs 16<sup>d</sup> |
| [30]   | 110             | 15-62                | Acute leukemias, MDS, MM, lymphomas | Myeloablative | 60% vs 34%<sup>1</sup>, (4 yr) | NA                  | 13% vs 18%<sup>2</sup>, (3 yr) | 28% vs 41%<sup>2</sup>, (grades 2-4) | 37% vs 52%<sup>2</sup>, (grades 2-4) | 45% vs 61%<sup>2</sup>, (All cGVHD) | 16% vs 28%<sup>a</sup>, (extensive cGVHD) | 20 vs 15<sup>d</sup> | 38 vs 25<sup>d</sup> |
| [14]   | 72              | 18-61                | CML | Myeloablative | 72% vs 81%<sup>2</sup>, (3 yr) | 65% vs 81%<sup>2</sup>, (3 yr) | 15% vs 0%<sup>1</sup>, (3 yr) | 20% vs 19%<sup>2</sup>, (grades 2-4) | 49% vs 55%<sup>2</sup>, (grades 2-4) | 30% vs 59%<sup>2</sup>, (extensive cGVHD) | 22 vs 17<sup>d</sup> | 21 vs 142 |

<sup>1</sup>Different conditioning regimens; <sup>2</sup>Not statistically significant; <sup>3</sup>P < 0.05, <sup>4</sup>P < 0.01, <sup>5</sup>P < 0.001. GVHD: Graft-versus-host disease; PBSC: Peripheral blood stem cell; HLA: Human leukocyte antigen; BM: Bone marrow; CML: Chronic myeloid leukemia; MDS: Myelodysplastic syndrome; MM: Multiple myeloma; NHL: Non-Hodgkin lymphoma; PMF: Primary myelofibrosis; AML: Acute myeloid leukemia; CLL: Chronic lymphocytic leukemia; Bu/Cy: Busulfan and cyclophosphamide; NA: Not available.
and cytomegalovirus (CMV) status, etc. If the recipient is CMV seronegative, CB transplant might be preferred as it is less likely to transmit CMV infection and CMV seronegative donor might not be easily available. Good clinical evidence guiding selection of stem cells for HSCT in patients with hematological malignancies is summarized in the following section.

**CLINICAL EVIDENCE FOR SELECTION OF STEM CELL SOURCE IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES**

**HLA-matched related donor**

There were a number of randomized controlled trials (RCTs) comparing PBSC and BM as stem cell source in transplants using HLA-matched related donor for patients with hematological malignancies. They are summarized in Table 2. There were no clinical trials comparing HLA-matched related CB with either BM or PBSC.

Most of the RCTs comparing matched related donor BM and PBSC transplantation for patients with hematological malignancies found no significant differences between the two stem cell source in important outcomes including overall survival, disease-free survival, transplant-related mortality, relapse, acute GVHD and chronic GVHD. However, all trials showed significantly faster neutrophil engraftment in PBSC transplants, and all but one trial showed significantly faster platelet engraftment in PBSC transplants, which may result in earlier hospital discharge for PBSC recipients and lower cost for PBSC transplantation. Lymphocyte recovery was also found to be better in the PBSC group in one trial.

There was one trial showing significantly better overall survival at 30 mo in patients who received PBSC compared with BM. Yet another trial showed opposite result, with better overall survival in BM recipients. However, in this trial CD34 selection was done before stem cell infusion in both BM and PBSC products and PBSC recipients happened to receive more CD34+ cells and T cells. Overall survival at 4 years was significantly worse in the PBSC group compared with the BM group, largely due to increased GVHD and TRM in PBPC recipients receiving T-cells greater than 2 × 10^9/kg. Acute GVHD appeared strongly associated with increased TRM. Higher number of CD34+ cells was associated with less TRM.

Some trials showed significantly higher probability of relapse in BM recipients than in PBSC recipients, which might translate into better disease-free survival in PBSC transplants compared with BM transplants. The differences in disease-free survival appeared more pronounced among patients with higher risk malignancies, “High risk” or “late stage” hematological malignancies usually include patients with acute leukemia in second or later remission, CML in blastic transformation, refractory anemia with excess of blasts in transformation, and lymphoma heavily pretreated with chemotherapy or autologous transplants.

Some trials showed PBSC recipients had significantly more grade 2-4 acute GVHD, chronic GVHD and extensive chronic GVHD compared with BM recipients, which resulted in significantly more patients who underwent PBPC transplant needed immunosuppressive treatment, and longer periods of corticosteroid use and hospitalization. There was no difference in performance status, return to work, incidence of bronchiolitis obliterans, hematopoietic function, and secondary malignancies between the two groups in the long term in one trial. In contrast, another trial showed that late mortality due to chronic GVHD was more frequent in PBSC recipients compared with BM recipients.

There were 2 more RCTs that included a few patients with severe aplastic anemia in addition to patients with hematological malignancies. One small trial of 30 patients found that PBSC transplant resulted in significantly faster hematopoietic reconstitution, fewer days with neutropenic fever, shorter hospital stay and fewer acute GVHD (6.7% vs 46.7%) (21). Another trial of 57 patients found that the PBSC and the BM groups had similar overall survival at 18 mo (64% vs 67%), speed to neutrophil and platelet engraftment, and grade 2-4 acute GVHD (54% vs 52%) (22). However, PBSC transplant resulted in significantly more steroid refractory acute GVHD (32% vs 0%), chronic GVHD (90% vs 47%), extensive chronic GVHD (80% vs 22%) and longer requirement for immunosuppressive therapy (23).

A meta-analysis of 5 RCTs (9-12,24) showed that PBSC transplant had significantly higher risk of acute GVHD (RR = 1.23, 95%CI: 1.05-1.45) and chronic GVHD (RR = 1.37, 95%CI: 1.08-1.74) compared with BM transplant (24). A newer meta-analysis of 7 of RCTs (19-22) showed no difference in mortality between PBSC and BM transplants (OR = 0.81, 95%CI: 0.62-1.05) (25). However, mortality was significantly lower in PBSC recipients compared with BM recipients in studies that included more patients with intermediate or advanced disease (OR = 0.64, 95%CI: 0.45-0.91) (26). Subgroup analysis revealed no significant association between mortality and CD34+ cell dose.

Another meta-analysis of individual data of 1111 patients from 9 RCTs (both published and unpublished) found that there was no significant difference in overall survival between the PBSC and the BM groups but disease-free survival was significantly higher in the PBSC group (OR = 0.80, 95%CI: 0.67-0.97) (27). Subgroup analyses showed that both overall survival (OR = 0.64, 95%CI: 0.46-0.90) and disease-free survival (OR = 0.63, 95%CI: 0.45-0.87) were significantly better in patients with late stage disease who received PBSC compared with BM (27).

PBSC transplant led to significantly faster neutrophil engraftment (OR = 0.31, 95%CI: 0.25-0.38) and platelet engraftment (OR = 0.52, 95%CI: 0.44-0.61) compared with BM transplant (27). PBSC transplant was associated with a significant increase in grade 3-4 acute GVHD (OR = 1.39, 95%CI: 1.03-1.88), chronic GVHD (OR = 1.92, 95%CI: 1.47-2.49), and extensive chronic GVHD (OR = 1.89, 2013). Cheuk DKL. Stem cell source for HSCT
GVHD (RR = 0.70, 95%CI: 0.51-0.97) compared with acute GVHD (RR = 0.73, 95%CI: 0.64-0.82) and chronic and TRM (RR = 1.28, 95%CI: 1.03-1.58) was significantly lower in CB recipients compared with that after 7-8/8 allele-matched BM or PBPC transplant [45]. However, TRM was significantly higher after CB transplant than after 8/8 allele-matched BM transplant (HR = 1.69, 95%CI: 1.19-2.39) or PBPC transplant (HR = 1.62, 95%CI: 1.18-2.23) [45]. Grade 2-4 acute and chronic GVHD were significantly lower in CB recipients compared with 7-8/8 allele-matched PBPC recipients (HR = 0.57, 95%CI: 0.42-0.77 and HR = 0.38, 95%CI: 0.27-0.53, respectively) [45]. Chronic but not acute GVHD was significantly lower after CB transplant than after 8/8 allele-matched BM transplant (HR = 0.63, 95%CI: 0.44-0.90) [45]. There was no difference among the stem cell sources in the rate of relapse [45].

One comparative study performed disease-specific analysis of the difference between CB transplant and BM transplant in 484 patients with AML and 336 patients with ALL after myeloablative conditioning [46]. Among AML patients, CB recipients had significantly lower overall survival (HR = 1.5, 95%CI: 1.0-2.0) and leukemia-free survival (HR = 1.5, 95%CI: 1.1-2.0) compared with BM recipients [46]. TRM and relapse did not differ significantly [46]. Among ALL patients, there was no significant difference between the groups in overall survival, leukemia-free survival, TRM, and relapse [46].

Another study compared unrelated CB transplants with unrelated donor BM or PBSC transplants in adults with ALL in first or second complete remission [46]. This study found no significant differences in the 3-year overall survival between CB (44%), matched (44%) and mismatched (43%) unrelated donor transplants. CB transplants had significantly slower engraftment and less grade 2-4 acute but similar chronic GVHD, disease-free survival, TRM, and relapse [46].

**OTHER IMPORTANT CONSIDERATIONS**

**Double cord blood**

In case a single CB unit has insufficient cell dose, 2 CB units can be used, but both are preferably at least 4/6 HLA-matched with the recipient and with each other, and together provide sufficient cell dose. Non-randomized studies comparing double CB transplant with single CB transplant in patients with hematological malignancies usually found that double CB transplant was associated with higher incidence of grade 2 acute GVHD [46-53], but there was no significant difference in overall survival, disease-free survival, chronic GVHD and engraftment times [46,52,53,56-59]. However, recently one study found superior overall survival and disease-free survival in addition to lower relapse in patients who received double CB compared with single CB transplant, although TRM

Unrelated donor

There was an RCT comparing PBSC and BM transplants using HLA-matched unrelated donors after myeloablative or reduced intensity conditioning in 551 patients with hematological malignancies. There was no significant difference between the PBSC and the BM groups in 2-year overall survival (HR = 1.06, 95%CI: 0.81-1.39), disease-free survival (HR = 1.04, 95%CI: 0.83-1.30), and TRM (HR = 1.08, 95%CI: 0.56-2.10) [31]. PBSC transplant resulted in significantly better neutrophil engraftment (HR = 2.08, 95%CI: 1.80-2.42) and platelet engraftment (HR = 2.77, 95%CI: 1.78-4.30), but significantly more grade 2-4 acute GVHD (HR = 0.75, 95%CI: 0.63-0.90), grade 3-4 acute GVHD (HR = 0.63, 95%CI: 0.47-0.84), chronic GVHD (HR = 0.70, 95%CI: 0.59-0.83), and extensive chronic GVHD (HR = 0.60, 95%CI: 0.39-0.91). PBSC recipients had significantly lower incidence of relapse (HR = 1.91, 95%CI: 1.34-2.74). A significant inverse relationship was observed between acute GVHD and overall survival.

95%CI: 1.47-2.42), but a significant decrease in relapse (OR = 0.71, 95%CI: 0.54-0.93) in both late stage disease (OR = 0.59, 95%CI: 0.38-0.93) and early stage disease (OR = 0.69, 95%CI: 0.49-0.98) [27]. Non-relapse mortality was not significantly different between the PBSC and the BM groups [27]. A decision analysis based on meta-analysis results [27] demonstrated the superiority of PBSC over BM in both overall and quality-adjusted life expectancy [28]. However, BM was found to be the more appropriate strategy if the 1-year relapse probability was below 5% [28].

The most recent meta-analysis which included 11 RCTs [27,14,15,20,22,26,30,38] found that PBSC and BM transplants had comparable overall survival (HR = 1.06, 95%CI: 0.81-1.39), disease-free survival (HR = 1.04, 95%CI: 0.83-1.30), and TRM (HR = 1.08, 95%CI: 0.56-2.10) [31]. PBSC transplant resulted in significantly better neutrophil engraftment (HR = 2.08, 95%CI: 1.80-2.42) and platelet engraftment (HR = 2.77, 95%CI: 1.78-4.30), but significantly more grade 2-4 acute GVHD (HR = 0.75, 95%CI: 0.63-0.90), grade 3-4 acute GVHD (HR = 0.63, 95%CI: 0.47-0.84), chronic GVHD (HR = 0.70, 95%CI: 0.59-0.83), and extensive chronic GVHD (HR = 0.60, 95%CI: 0.39-0.91). PBSC recipients had significantly lower incidence of relapse (HR = 1.91, 95%CI: 1.34-2.74). A significant inverse relationship was observed between acute GVHD and overall survival.

There was no RCT comparing unrelated CB with single CB transplant, although TRM was not significantly different in both overall and quality-adjusted life expectancy [28]. However, recently one study found no significant difference in overall survival, leukemia-free survival, TRM, and relapse [46].

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December 24, 2013 | Volume 3 | Issue 4 |
and chronic GVHD were not significantly different\[60\]. Double CB transplant was also found to be more cost-effective in terms of quality adjusted life years in adults with acute leukemia in first remission in France\[60\]. On the other hand, intrabone injection of single CB might be associated with faster engraftment (median 23 vs 28 d) and lower cumulative incidence of relapse (25% vs 29%) compared with intravenous double CB transplant\[41\].

There were some non-randomized studies comparing double CB transplant with BM or PBSC transplant from other donors. One study on 536 patients with hematological malignancies transplanted with myeloablative conditioning found that 5-year leukemia-free survival was similar in double CB transplant (51%) and other types of donors (either BM or PBSC), including matched related donor (33%), matched unrelated donor (48%), and mismatched unrelated donor (38%)\[61\]. Non-relapse mortality was highest for double CB (34%), compared with matched related donor (24%), matched unrelated donor (14%), or mismatched unrelated donor (27%)\[62\]. However, the risk of relapse was lowest in recipients of double CB (15%), compared with matched related donor (43%), matched unrelated donor (37%), or mismatched unrelated donor (35%)\[62\]. The risks of grade 2-4 acute GVHD and chronic GVHD were also the lowest for double CB (60% and 26%), compared with matched related donor (65% and 47%), matched unrelated donor (80% and 43%), or mismatched unrelated donor (85% and 48%)\[62\].

Another study on 367 patients with hematological malignancies after myeloablative or non-myeloablative conditioning found that 2-year overall survival, progression-free survival, TRM and grade 2-4 acute GVHD were not significantly different in double CB transplant (65%, 55%, 25% and 43%) as compared to related donor transplant (70%, 66%, 15%, and 27%) and unrelated donor transplant (62%, 55%, 27%, and 39%)\[63\]. However, late acute or chronic GVHD was significantly lower in double CB transplant (28%) as compared to related donor transplant (31%) and unrelated donor transplant (44%)\[63\].

A third study compared double CB transplant with 9/10 mismatched unrelated donor BM or PBSC transplants with reduced intensity conditioning for patients with hematological malignancies and found that double CB transplant was associated with lower incidence of extensive chronic GVHD at 2 years compared with unrelated donor transplant (6.4% vs 21.4%)\[64\]. However, both groups were comparable for 2-year overall survival (47.9% vs 52.3%), progression-free survival (43.3% vs 38.3%), TRM (26% vs 24.2%), relapse (34.3% vs 37.6%), grade 3-4 acute GVHD (19.1% vs 21.4%), and neutrophil engraftment time (median 17 vs 16 d)\[64\].

There were 3 studies comparing double CB transplant with unrelated donor PBSC transplants after reduced intensity conditioning for patients with hematological malignancies. The study by Le Bourgeois found that the 2 groups had similar 2-year overall survival (61% vs 62%), disease-free survival (50.5% vs 59.0%), relapse incidence (23.0% vs 35.5%), cumulative incidences of engraftment, grade 2-4 acute and chronic GVHD\[65\]. However, double CB recipients had significantly higher median time to platelet recovery (38 vs 0 d), early mortality before day +100 (20.5% vs 4.0%), and 2-year TRM (26.5% vs 6.0%) compared with PBSC recipients\[65\]. The presence of a lymphoid disorder was associated with a significantly higher overall survival\[65\]. The study by Chen found that the 3-year overall survival and progression-free survival were comparable between double CB and PBSC transplant (46% vs 50% and 30% vs 40%, respectively), but the cumulative incidence of TRM was significantly higher in double CB transplant (26.9% vs 10.4%)\[66\]. The cumulative incidence of grade 2-4 acute GVHD was not significantly different but the 2-year cumulative incidence of chronic GVHD was significantly lower in double CB transplant compared with PBSC transplant (21.9% vs 33.9%)\[66\].

The study by Jacobson found that there was no significant difference between double CB transplant and PBSC transplant in 2-year overall survival (66% vs 68%), progression-free survival (49% vs 57%), TRM (11% vs 11%), relapse (40% vs 32%) and grade 2-4 acute GVHD (21% vs 12%)\[67\]. Double CB recipients had significantly more infections (69% vs 33%), both viral (29% vs 1%) and bacterial (50% vs 8%) infections, but significantly less chronic GVHD (24% vs 54%)\[67\]. Reconstitution of T cells was significantly delayed in double CB recipients compared with PBSC recipients for 1-6 mo post-transplant, including naive and memory CD4+ T cells, regulatory T cells, and CD8+ T cells\[67\]. In contrast, B cells recovered more rapidly in double CB recipients and B cell number remained significantly greater at 3-24 mo post-transplant\[67\]. Natural killer (NK) cells also recovered more rapidly in double CB recipients and remained significantly greater at 1-24 mo post-transplant\[67\].

**Haploidentical donor**

HLA-haploidentical related donor is an important alternative if no matched related donor is available\[68\]. Either PBSC or BM can be the stem cell source for haploidentical transplant. Positive selection of CD34+ stem cells from harvested PBSC and infusion of high doses of stem cells successfully overcame HLA barrier with good engraftment rate and low incidence of GVHD\[69-78\]. Leukemia-free survivals and relapses were better in transplants performed in larger centers\[70\], and in transplants with natural killer cell killer immunoglobulin like receptor (KIR) mismatch\[88\]. However, infection risk was high as immune reconstitution was slow with purified CD34+ cells. Subsequently, negative stem cell selection with depletion of CD3+ T cells with or without depletion of CD19+ B cells achieved similar success of engraftment without excessive GVHD with myeloablative or reduced intensity conditioning\[81-86\]. Immune recovery with this method was notably faster with reduced infections\[81,83,86\]. Unmanipulated T cell replete PBSC and/or BM products could also achieve reasonably good results with intensive GVHD prophylaxis or post-transplant cyclophospha-
CONCLUSION

In conclusion, existing high level evidence suggest that there is no significant advantage of PBSC over BM in HLA-matched sibling transplant for patients with hematological malignancies. PBSC transplant probably results in lower risk of relapse and hence better disease-free survival, especially in patients with high risk or late stage disease at the expense of higher risks of both severe acute and chronic GVHD. Existing data are insufficient or inconclusive for firm conclusions in specific subgroups such as a particular disease entity, conditioning regimen or in children. High level evidence is scarce in the unrelated donor setting. The only RCT available suggests that PBSC and BM result in comparable overall and disease-free survivals in patients with hematological malignancies; and PBSC transplant results in lower risk of graft failure but higher risk of chronic GVHD. High level evidence is lacking for CB in comparison to BM or PBSC. The risks and benefits of different sources of stem cells likely change with different conditioning regimen, strategies for prophylaxis and treatment of GVHD and manipulation of grafts. The recent success and rapid advance of double CB transplant and haploidentical BM and PBSC transplants further complicate the selection of optimal stem cell source. Novel therapies for treatment and prophylaxis of GVHD also minimize the key differences between stem cell sources. Advances in graft manipulation and cellular therapies might change the whole paradigm making stem cell source selection less critical, e.g., stem cell enrichment could facilitate engraftment, specific and highly selective depletion of certain lymphocyte subsets and alloreactive cells could minimize GVHD; infusion of mesenchymal stem cells could facilitate engraftment and reduce GVHD; titrated T cell dosing and NK cell therapy might reduce relapse. Detailed counseling of patient and donor regarding risks and benefits in the specific context of the patient and transplant method is of paramount importance for informed decision making.

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