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Peripheral Blood Stem Cell Transplantation as an Alternative to Bone Marrow Transplantation: An Overview

Nalini Janakiraman, MD*

Stem cells capable of restoring hematopoiesis following lethal bone marrow injury circulate in the blood of many animals, including humans. When collected through leukapheresis and reinfused following high-dose chemotherapy, stem cells offer a treatment option not currently open to some patients who are unable to undergo autologous bone marrow transplantation because of tumor involvement in the pelvis, prior pelvic radiation, or intolerance to general anesthesia. After stem cell infusion, hematologic and immunologic recovery are rapid in comparison to that after autologous bone marrow reinfusion; however, in some cases platelet engraftment is slower. There is some evidence that tumor contamination in the peripheral blood is much less than in the marrow. In any event, most relapses of malignant disease occur at the site of origin and represent treatment failure rather than growth of reinfused malignant cells. Prospective controlled trials are needed to evaluate stem cell in comparison to autologous bone marrow transplantation. (Henry Ford Hosp Med J 1991;39:103-7)

Hematopoietic stem cells capable of restoring hematopoiesis when infused following lethal bone marrow injury are known to circulate in the blood of many animals, including non-human primates (1,2). Many bone marrow transplant centers now use stem cells obtained from peripheral blood by leukapheresis as an alternative to bone marrow transplantation in some situations (3-5).

Hematopoiesis and Peripheral Blood Stem Cells

The hierarchy of the hematopoietic system is depicted in the Figure. The pluripotent stem cells are capable not only of differentiation along different lines but also of self-renewal. These cells are essential for successful engraftment following high-dose chemotherapy. There is currently no assay to measure these cells, and we do not understand fully their phenotypic characteristics. Cultures now performed in the laboratory, e.g., colony-forming unit–granulocyte erythroid macrophage megakaryocyte (CFU-GEMM), colony-forming unit–granulocyte macrophage (CFU-GM), and burst-forming unit–erythrocyte, measure more committed cells. CD-34 antigen, an antigen expressed on the surface of stem cells, is used as a marker, but it may be a marker for a cell which is derived by several multiplications beyond the stem cell, closer to the more committed cells.

Studies in mice, dogs, and baboons have shown that hematopoietic cells capable of engraftment circulate in peripheral blood. Multiple canine studies (6) have demonstrated the feasibility of obtaining such cells by apheresis and utilizing them to reconstitute hematopoiesis after lethal radiation. Ample evidence shows that stem cells can also be obtained from the peripheral blood of human beings. In chronic granulocytic leukemia, cells obtained by leukapheresis during the chronic phase have been used for successful engraftment during blast crisis treated by myeloablative chemotherapy (7). A prospective study of the treatment of aplastic anemia by allogeneic bone marrow transplantation with and without donor buffy coat cells showed that the addition of buffy coat cells reduced the rejection rate (8). A high rate of sustained graft and of acute and chronic graft versus host disease confirmed engraftment of peripheral blood stem cells. Blood-derived granulopoietic proliferation can be sustained in long-term cultures (up to eight weeks) with generation of CFU-GM cells similar to that of bone marrow cells, despite some qualitative differences (9). Finally, an increasing number of patients are now being treated with high-dose chemotherapy and autologous peripheral blood stem cell reinfusion.

Long-term Engraftment with Peripheral Blood Stem Cells

In the absence of some form of cell tagging, it is difficult to prove that the hematopoietic recovery is from infused bone marrow or peripheral blood stem cells and is not spontaneous. Because the myeloablative regimen is the same as that used prior to allogeneic transplantation, recovery almost certainly results from the engraftment of infused cells. Several reports of follow-
Advantages of Peripheral Blood Stem Cells

In patients who have had radiation therapy to the pelvis or who have tumor involvement of the pelvic bone, the bone marrow harvest site, collection of peripheral blood stem cells by leukapheresis offers a means to obtain stem cells. This is also true for patients with contraindications to general anesthesia. Any other advantages to peripheral blood stem cells are not well established. It is believed, but not yet proved, that there are fewer malignant cells in the peripheral blood than in the bone marrow. This is difficult to establish because of many complex variables such as the different biology of tumors, varied microenvironment between the bone marrow and peripheral blood, and the unreliability of methods for comparing the bone marrow and peripheral blood. With both autologous bone marrow and peripheral blood stem cell transplantation, failure to eradicate the disease is a much greater problem than the reinfusion of malignant cells. Most relapses occur at sites of original disease and are not disseminated disease which would be consistent with reinfusion of malignant cells. If more effective therapy could eliminate residual disease, autologous bone marrow could be compared to the use of peripheral blood stem cells more accurately.

More rapid hematologic recovery may follow peripheral blood transplantation compared to bone marrow transplantation (11). Because hematologic recovery is earlier by several days, the risk of infection, the mortality, and the length of hospital stay are reduced. Earlier recovery is attributed to the reinfusion of more committed cells than are provided by the bone marrow. Immunologic reconstitution is also more rapid with peripheral blood stem cell transplantation compared to autologous bone marrow transplantation (11,12).

Peripheral Blood Stem Cell Collection

Stem cells are collected by repeated leukapheresis either at random for several consecutive days (steady state collection) or during recovery from chemotherapy-induced myelosuppression (recovery phase collection). A single leukapheresis in a healthy individual will yield $0.3 \times 10^6$ CFU-GM/kg. About 20 to 30 steady state collections are needed to obtain the number of CFU-GM obtained from bone marrow harvest. This time-consuming procedure may be the only option for some patients who have been extensively pretreated. Kessinger et al (13) required a median of 8 (range 6 to 17) steady state leukaphereses to collect $0.6 \times 10^6$ (0 to 98.6) CFU-GM/kg. The granulocyte and platelet engraftment durations were similar to autologous bone marrow transplant (25 days).

Richman et al (14) reported in 1976 that during recovery from chemotherapy-induced neutropenia the circulating granulocytic stem cells (colony-attaching unit—culture) increased from 6 to 23 per $2 \times 10^5$ mononuclear cells plated. Cytocic changes in the concentration of stem cells with a maximum value of 20 times the baseline were demonstrated. They estimated that enough stem cells for transplant could be obtained from the peripheral blood by appropriately timed 17 liter leukapheresis.

This information stimulated the increasing use of peripheral blood stem cell transplantation. The number of stem cells collected following induction and consolidation therapy for acute myelogenous leukemia (AML) in very early remission was adequate for transplantation after myeloablative chemotherapy (15). Moderately intensive chemotherapy was used to facilitate stem cell collection in other disease states, i.e., cyclophosphamide 1.5 or 4 g/M^2, doxorubicin 90 mg/M^2, and vincristine 1.4 mg/M^2 administered to patients with multiple myeloma (2). The median number of leukaphereses needed for recovery phase collection was 4 (range 2 to 6). Use of recovery phase collections resulted in more rapid engraftment of granulocytes.

Recently the hematopoietic growth factors have been used to increase the number of CFU-GM obtained from peripheral blood (16,17), but confirmatory long-term follow-up is needed.

After counting the total number of nucleated cells, the cells are cultured on soft agar to determine the number of CFU-GM. This measure of the stem cell load generally correlates with time to engraftment. However, the CFU-GM assay requires 14 days. Some patients may be apheresed unnecessarily if the CFU-GM
assay subsequently discloses no increase in peripheral blood stem cells. A more rapid assay is needed to facilitate decisions regarding the timing and number of leukaphereses. The number of CD-34-positive mononuclear cells in the collection seems to correlate with peripheral blood CFU-GM, and the test is utilized in some centers (1).

Procedure

Different machines (Hemonetics V50, Fenwall CS3000) are used for leukapheresis (18,19). A protocol aimed at collecting lymphocytes is generally used and a large venous access is required. In steady state collections, the patients undergo leukapheresis on consecutive days, usually five times a week, until enough stem cells are obtained (18,20).

In recovery phase collections, different parameters are used to time the leukapheresis. Total monocyte count of 1,000/μL or 30% of WBC is generally a good indicator of the beginning of the peak of circulating stem cells. Minimal or no bone marrow involvement and a rise in WBC from 1,000 to 3,000/μL in less than five days are independent variables predictive of high CFU-GM collections. The extent of prior chemotherapy does not always influence the wealth of the collections (15).

Interlabatory variations in the CFU-GM assay may explain the lack of consensus as to the minimum CFU-GM cell dose needed for hematopoietic reconstitution. Usually a CFU-GM dose of more than 30 x 10^6/kg is always associated with engraftment. In contrast, 1 to 2 x 10^9/kg of CFU-GM cells are needed for autologous bone marrow engraftment. The need for this high CFU-GM dose is not known; apparently the peripheral blood contains fewer stem cells relative to the committed (CFU-GM) cells. Moreover, the accessory (bone marrow) cells needed for engraftment may be lacking in peripheral blood.

The product is processed either by elutriation (a type of physical separation), repeat apheresis, or density gradient separation. More efficient means of collection and cryopreservation are needed.

Risks of peripheral blood stem cell transplantation are primarily related to the total volume infused and red cell contamination. They include hemoglobinuria (92%), hematuria (80%), elevated serum bilirubin (43%), elevated serum creatinine (15%), and increase in pulse rate (61%). They are generally mild and reversible (21). The volume infused is greater in steady state collections and the red cell contamination is least with density gradient separations. More efficient means of collection and cryopreservation are needed.

Hematopoietic Recovery After Peripheral Blood Stem Cell Autograft

The Table contains hematopoietic recovery data on peripheral blood stem cell transplantations done for different disease states in different centers (2,13,22-24). As use of the procedure is very recent, most of these data were published after 1986. Only one major center employs steady state leukapheresis, and its engraftment is similar to that of autologous bone marrow transplantation. All others utilize recovery phase collections, requiring fewer than 5 leukaphereses. The CFU-GM collected is 10 to 100 times greater than in steady state collections. Rapid granulocyte engraftment occurred with all recovery phase collections. Platelet engraftment is generally acceptable, although delay or failure to engraft platelets has been reported (24), unlike experience with autologous bone marrow transplantation.

Juttner et al (22) reported a reduction in platelet counts occurring after three to six weeks followed by gradual recovery. Explanation of this observation is not clear, but this secondary fall in platelet count did not occur after non-AML transplantations. Perhaps there is endogenous platelet recovery after six weeks, or cryopreservation may selectively destroy more committed cells, causing the transient thrombocytopenia.

Successful engraftment correlates with the cell dose infused (25). Successful hematopoietic reconstitution was observed in all five patients infused with ≥ 30 x 10^6 CFU-GM/kg but in only two of nine cases infused with fewer cells. On the other hand,

<table>
<thead>
<tr>
<th>Disease States</th>
<th>Number of Patients</th>
<th>Steady State Recovery Phase</th>
<th>Leukaphereses (Range)</th>
<th>MNC/kg (Range)</th>
<th>CFU-GM/kg (Range)</th>
<th>ANC 500</th>
<th>Platelet &gt; 20,000</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoma</td>
<td>40</td>
<td>Steady state</td>
<td>8</td>
<td>7.03 x 10^6 (4.51-16.36)</td>
<td>0.6 x 10^6 (0.98-14)</td>
<td>25 days (11-12)</td>
<td>25</td>
<td>7 patients died prior to recovery of HS</td>
</tr>
<tr>
<td>AML</td>
<td>12</td>
<td>Induction</td>
<td>4</td>
<td>5.3 x 10^6 (2.6-3)</td>
<td>88 x 10^4 (15-149)</td>
<td>11</td>
<td>13</td>
<td>5 received BM also</td>
</tr>
<tr>
<td>NHL</td>
<td>3</td>
<td>Recovery</td>
<td>NA</td>
<td>3.2 x 10^6 (3.5)</td>
<td>34 x 10^4 (48-81)</td>
<td>12</td>
<td>13</td>
<td>cy-GM</td>
</tr>
<tr>
<td>Myeloma</td>
<td>13</td>
<td>Recovery</td>
<td>NA</td>
<td>2.9 x 10^6 (0.1-18.9)</td>
<td>16 (11-150)</td>
<td>25 days (50,000)</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Myeloma</td>
<td>8</td>
<td>Recovery</td>
<td>3-4</td>
<td>2.6 x 10^6 (11-12)</td>
<td>5.5 x 10^4 (2.2-13)</td>
<td>16</td>
<td>13</td>
<td>Significant delay in platelet HES</td>
</tr>
<tr>
<td>SCLC</td>
<td>4-BCNU</td>
<td>Recovery</td>
<td>4-5</td>
<td>3.8 ± 2 x 10^8 (11.4 ± 9.9 x 10^4)</td>
<td>13,14,14</td>
<td>15,44,48+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

bone marrow autografts are successful with 1 to 2 × 10^4 CFU-GM/kg. This may be evidence of the poor engrafting efficiency of peripheral blood stem cells but could result from a function of monocytes in the CFU-GM plates or the paucity of stromal cells in the peripheral blood to facilitate engraftment.

**Failure to Engraft**

Failure to engraft following autologous peripheral blood stem cell transplantation has been reported only twice (26,27). However, by today’s standards, too few CFU-GM were reinfused in both cases (3.4 × 10^4 and 6.7 × 10^4 CFU-GM/kg).

**Results of Peripheral Blood Stem Cell Transplantations in Acute Leukemias**

Three major studies, all from outside the United States, have reported on peripheral blood stem cell transplantations. Reiffers et al (28) from France initially treated nine patients who were in their second complete remission (CR). Two of these patients are alive and in continuous complete remission (CCR) with follow-up longer than three years. Encouraged, the authors reported the treatment of 26 AML patients in first remission. Two died early, 13 had leukemic relapse (12 of whom died within a year after peripheral blood stem cell transplantation), and 11 patients are in CCR with a median follow-up of two years. Estimated three-year disease-free survival is 33%.

Korbling et al (29) from Germany published the first single institution comparison of peripheral blood stem cell transplantation versus autologous bone marrow transplantation. Twenty patients were treated with peripheral blood stem cells collected either during recovery phase or using CSF-GM. Twenty-three patients received autologous bone marrow purged with methylprednisolone. The groups were comparable in age, sex, histologic subtype (French-American-British classification), WBC count, and duration of prior CR. Treatment in both groups consisted of cyclophosphamide and total body irradiation. The peripheral blood stem cell transplant group had earlier WBC recovery and a shorter hospital stay. There was no difference between the two groups in platelet recovery or disease-free survival. One death occurred in the autologous bone marrow transplant group and there were no deaths in the peripheral blood stem cell transplant group. Median follow-up was 29 months (peripheral blood stem cell) and 55 months (autologous bone marrow transplantation).

Juttner et al (1) from Australia published their results of peripheral blood stem cell transplantation in AML. Collections were performed during very early remission following induction and consolidation. Of the nine patients treated in second remission, all achieved a CR but all relapsed 2 to 14 months later. Hematopoiesis was maintained in all. Twenty-two patients with AML were treated in first remission at a median of 80 days after CR. Busulfan and cyclophosphamide were administered for myeloablation. Two patients died in remission, one of congestive heart failure on day 13, and the other of herpes zoster on day 23. Ten patients relapsed in 77 to 476 days while ten remain in CCR for a median duration of 111 days (range 48 to 643 days).

All experienced rapid neutrophil recovery and 18 of the 22 had prompt platelet recovery. One patient required reinfusion of bone marrow at six months because of continued platelet deficiency. The results from this study are comparable to the same authors’ results with autologous bone marrow transplantation.

Peripheral blood stem cell transplantation in acute leukemia appears to be at least as effective as autologous bone marrow transplantation. The stem cells can be collected easily during recovery phase from induction and consolidation. More definitive results await studies on more patients and longer follow-up.

**Other Malignancies**

This source of stem cells could reasonably be used for all other bone marrow transplantation indications.

Multiple myeloma is a chemotherapy-responsive B-cell neoplasm but is incurable with currently available regimens. Several attempts at allogeneic and autologous bone marrow transplantation appear promising. Because of the older age of the patients, autologous bone marrow transplantation is preferred. However, multiple myeloma is a malignancy of the bone marrow, and possible therapy with high-dose chemotherapy followed by autologous peripheral stem cell transplantation is appealing. Active research is in progress (2).

Other chemotherapy-responsive solid tumors such as breast cancer could also be treated with escalated doses of chemotherapy and autologous stem cell rescue. Frequent involvement of bone marrow by such malignancies suggests that peripheral blood may be a safer alternative as the source of stem cells.

**Summary**

Adequate pluripotent stem cells capable of sustained hematopoietic engraftment can certainly be obtained from peripheral blood by repeated leukapheresis. In situations such as bone marrow contamination by malignant cells, radiation to the harvest site, or serious donor risk, peripheral blood may be the only source of stem cells. Despite the discussed advantages, peripheral blood will not likely replace bone marrow as the major source of stem cells.

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**References**


