Is There an Increased Risk of Graft-Versus-Host Disease After Allogeneic Peripheral Blood Stem Cell Transplantation?

To the Editor:

Over the last few years, there has been an increasing use of allogeneic peripheral blood stem cell transplantation (alloPBSCT) to provide hematologic rescue after myeloablative therapy for the treatment of various malignancies.[1] Although the first results are encouraging, the cell content of the infused product and its effect on engraftment and immunologic recovery is still under discussion. Advantages of using mobilized PBSCs rather than bone marrow include the relative ease of collection and the rapid hematologic reconstitution compared with bone marrow. In general, alloPBSCTs have contained 3 to 4 times more $CD34^+$ and 1 to 2 logs more T cells than bone marrow bringing the increased risk of graft-versus-host disease (GVHD).[2]

Bensinger et al[3] reported the results of their initial experience by the use of alloPBSCT in various malignancies. All donors received 5 days of human granulocyte colony-stimulating factor (rhG-CSF; 5 μg/kg/d subcutaneously [SC]) and were leukapheresed for 2 days. Their preliminary results indicate that alloPBSCT mobilized by rhG-CSF can provide rapid hematologic recovery without greater incidence of acute GVHD.

Since 1993, 13 alloPBSCTs have been performed in our clinic. Our first experience was reported previously.[4] Seven patients were male and six were female. The median age was 27 years (range, 17 to 40 years). Patients' diagnoses were as follows: 7 acute myeloblastic leukemia (AML) in first complete remission, 3 chronic myelogenous leukemia (CML) in chronic phase, 2 acute lymphoblastic leukemia (ALL) in first and third relapses, and 1 aplastic anemia (AA). All the patients received PBSCs from their HLA-identical siblings. In 4 of the patients, alloPBSCT was used as a second procedure. In 2 of them, it was used for the failure of the first allogeneic bone marrow transplantation (alloBMT, the AA patient showed primary engraftment failure and the CML patient initially had engraftment, but he later showed engraftment failure due to grade II GVHD). Two other patients, an AML and an ALL patient, underwent alloPBSCT 20 and 6 months after alloBMT, respectively, because of disease recurrence. The characteristics of the patients is given in Table 1.

PBSC enrichment of the donors. G-CSF (Neupogen; Amgen, Thousand Oaks, CA) was used for the priming of the donors in various doses (2.5 μg/kg/d SC for 10 days [2 patients], 10 μg/kg/d SC for 5 days [6 patients], and 15 μg/kg/d SC for 5 days [5 patients]). All the donors were the HLA-identical siblings of the patients.

PBSC collection. For the 10-days schedule of G-CSF, leukapheresis was started on day 6; otherwise, it started on day 5. PBSCs were collected by apheresis from normal donors by using continuous flow blood separation (Cobe Spectra [COBE BCT, Inc, Lakewood, CO] or Fenwall CS 3000 [Baxter Healthcare Systems, Deerfield, IL]). A total of 33 leukapheresis were performed for the 13 donors. The median number of apheresis procedure for each patient was three.[1-3] No adverse effects due to apheresis were seen, except for transient episodes of parasthesia caused by citrate that responded promptly to calcium gluconate infusion. Patients received a median of 12.5 (range, 4.2 to 38.2) $\times$ 10^8/kg mononuclear cells or 33.6 (range 2.4 to 90.0) $\times$ 10^6/kg $CD34^+$ cells. Cells were administered directly to patients without cryopreservation.

CD34 assay. The yield of stem cells collected was assessed by the number of mononuclear cells in the harvest material and by the percentage of CD34 positivity among the collection of mononuclear cells. It was assessed by flow cytometry (Becton Dickinson, San Jose, CA).

Conditioning regimens. Ten patients were conditioned with busulfan at 4 mg/kg/d orally (PO) on 4 divided doses on days −8, −7, −6, and −5 and cylophosphamide at 60mg/kg/d intravenously (IV) on days −4 and −3. On day 0, harvest materials were administered to patients via central venous Hickman catheter. The AA patient was conditioned with the sequential use of antilymphocytic globulin plus cyclophosphamide (CY). One of the ALL patients received the CBV protocol (CY at 1.5 g/m^2/d on days −5 through −2, etoposide at 125 mg/m^2/d on days −5 through −2, and BCNU at 300 mg/m^2 on day −2) and the other received sequential application of cytosine arabinoside plus mitoxantrone plus etoposide.

Table 1. Patient Characteristics, Number of Cells Administered, and the Engraftment Days for alloPBSCT

Patient No.	Dx	MNC ($\times 10^8$/kg)	CD34$^+$ ($\times 10^6$/kg)	GVHD (grade)	ANC (day) (>0.5 × 10^9/L)	ANC (day) (>1.0 × 10^9/L)	PLT (day) (>20 × 10^9/L)	PLT (day) (>50 × 10^9/L)	Short-term Results (days)
UPN1	CML	5.45	35.0	2	16	19	18	25	+161
UPN2	AML	4.2	5.85	2	11	12	14	15	+265
UPN3	AML	16.0	19.0	2	14	15	13	14	+238
UPN4	AML	5.45	33.6	—	13	15	32	35	+214
UPN5*	AML	5.2	90.0	—	—	—	—	—	Early death
UPN6	AML	29.3	85.7	—	10	11	9	14	+168
UPN7	CML	8.1	88.0	2	10	15	—	—	+159
UPN8†	AML	17.5	82.5	—	—	—	—	—	Early death
UPN9	CML	14.0	NA	—	11	13	16	20	+130
UPN10	AML	38.2	—	—	11	12	12	15	+124
UPN11	ALL	12.5	10.8	2	12	14	15	16	+201
UPN12‡	ALL	4.8	2.4	4	31	38	31	37	65
UPN13§	AA	10.4	12.1	—	—	17	—	26	43

Abbreviation: NA, not available.

* He was lost on day +18 due to venoocclussive disease.

† She was lost with a cerebrovascular accident on day +15.

‡ He was lost due to grade IV acute GVHD.

§ He was lost due to massive hemoptysis on day +43.

Prophylaxis and treatment of GVHD. Diagnosis and grading of acute GVHD was based on accepted clinical criteria. Patients were evaluated for acute GVHD if they survived 21 days and had an evidence of engraftment. Chronic GVHD was evaluated if they survived more than 90 days with a persistent engraftment. Cyclosporine-A (CsA) plus short-course MTX were used for GVHD prophylaxis. MTX was omitted only during severe mucositis.

Hematopoietic engraftment and patient management after alloPBSCT. Median leukocyte engraftment was seen on day 11 (range, day 10 to 31) and platelet engraftment was on day 18 (range, day 14 to 37). All patients received a median number of 2 (range, 0 to 10) red blood cell transfusions and a median number of 4 (range, 1 to 12) platelet transfusions.

GVHD. Eleven patients were evaluable for the occurrence of GVHD. In 6 of them (54.5%), grade II-IV acute GVHD was observed. Five of them needed pulse steroid therapy because of progressive GVHD. One of them was lost due to grade IV GVHD. Although it is too early to say, none of our patients showed chronic GVHD.

Outcome. Median follow-up is 168 (range, 124 to 265) days. Four patients were lost. The AA patient was lost on day +43 with massive hemoptysis with a fully engrafted bone marrow. One of the AML patients was lost on day +10 due to venoocclusive disease and hepatic failure. Another AML patient was lost due to cerebrovasculer accident. An ALL patient who relapsed 6 months after alloBMT was lost due to acute grade IV GVHD. Nine patients are still alive with full engraftment and free of their disease.

Bensinger et al's study[3] and our study have shown the feasibility of using allogeneic PBSCs collected after the administration of G-CSF from normal donors. High doses of CD34 cells obtained by PB mobilization can improve the speed of hemapoietic recovery. In our study, median granulocyte and platelet engraftments were on days 11 (range, day 10 to 31) and 18 (range, day 14 to 37), respectively. These parameters can even compete with our historical autologous bone marrow or autologous PBSC engraftment days. Our historical alloBMT patients had engraftment for granulocytes and platelets on days 17 (range, day 11 to 30) and 27 (range, day 18 to 65), respectively. It is clear that alloPBSCT gives the advantage for early engraftment. In parallel with this finding, the number and duration of febrile neutropenic episodes, the use of antibiotics, the number of hospital days, and the cost of allogeneic transplant decrease.

On the other hand, because alloPBSCs contains 1 to 2 logs of more T cells than does bone marrow, the transfer of large numbers of lymphocytes by alloPBSCT brings the increased risk of GVHD. In clinical studies, this adverse effect has been shown. This problem has been attempted to be solved with the removal of T cells and the selection of CD34$^+$ cells. Separating T cells subsets to maximize graft-versus-leukemia effect and minimize GVHD incidence is another approach. In our study, we have 54.5% (6/11) of acute GVHD. Except for one of them, all 5 of the other patients needed pulse steroid therapy. This incidence was 33.7% in our 80 historical alloBMT patients transplanted from an HLA-matched sibling donors. Using the data given above, there seems to be an increased risk of GVHD with the use of alloPBSCT. On the contrary, the effect of GVHD on disease outcome and survival by inducing graft-versus-leukemia effect is not clear yet. Because our follow-up time is limited, no results can be given for chronic GVHD.

As a result, alloPBSCT is an alternative for alloBMT because of the ease of collection and rapid hematologic recovery. However, the net advantage of this maneuver related to GVHD is not clear yet, as Bensinger et al[3] have reported.

Haluk Koç
Günhan Gürman
Önder Arslan
Muhit Özcan
Hamdi Akan
Osman İlhan
Nahide Konuk
Meral Beksaç
Akin Uysal
Ankara University
Faculty of Medicine
Ibni Sina Hospital
Department of Hematology-Oncology
Bone Marrow Transplantation Unit
Ankara, Turkey

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