The Korean Journal of Internal Medicine
Vol. 13, No. 1, February, 1998

A Case of Chronic Graft-versus-Host-Disease Following Allogeneic Peripheral Blood Stem Cell Rescue for Poor Graft Function after Bone Marrow Transplantation

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To overcome poor graft function after allogeneic bone marrow transplantation (BMT), the use of peripheral blood stem cells (PBSC) instead of bone marrow is gaining more popularity because of its advantages. There may, however, be an increased risk of graft-versus-host-disease (GVHD) because of the large number of lymphocytes present in a leukapheresis product.

An 18-year-old man with severe aplastic anemia underwent an allogeneic BMT using his HLA-identical sister. After initial excellent graft take for 8 months, his blood counts gradually decreased to 2.8 X 10^9/L of white cells and 28 X 10^9/L of platelets with marrow cellularity of <10%. After allogeneic granulocyte-colony stimulating factor mobilized PBSC rescue, the patient's blood counts recovered satisfactorily. Around 1 year after the boost, he developed chronic GVHD that responded to prednisolone and cyclosporin A. He is now well on low-dose steroids at day +1055 after PBSC rescue. The present case is the first experience of a long-term follow-up who underwent allogeneic PBSC rescue in Korea.

Key Words : *Severe aplastic anemia; Bone marrow transplantation; Poor graft function; Peripheral blood stem cells; Graft-versus-host-disease*

INTRODUCTION

Although bone marrow transplantation (BMT) can be a successful treatment modality for a variety of hematological disorders, malignancies and metabolic defects, a number of obstacles to be overcome still exist for a better outcome with the transplantation technique. Patients with engraftment failure or poor graft function following allogeneic BMT are at high risk of morbidity and mortality. Therapy of engraftment failure or poor graft function includes the administration of human recombinant growth factors[1] and reinfusion of donor marrow.

Recently, infusion of allogeneic peripheral blood stem cells (PBSC) mobilized by granulocyte-colony stimulating factor (G-CSF) has been used in patients with graft failure after allogeneic BMT[2]. Allogeneic PBSC transplantation has some advantages over allogeneic BMT: general anesthesia is not required to collect hematopoietic stem cells and faster hematologic recovery has been reported. There may, however, be an increased risk of graft-versus-host-disease (GVHD) as leukapheresis products usually contain 1 log higher T lymphocytes than bone marrow[2-4]. Here we report a case of a long-term follow-up who developed chronic GVHD following allogeneic PBSC rescue for poor graft function after allogeneic BMT.

CASE

An 18-year-old man with severe aplastic anemia, who

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was diagnosed in June 1991, underwent an allogeneic BMT from his HLA-identical 21-year-old sister. The patient was positive for HBsAg and HBeAg, but liver enzymes were normal. The conditioning regimen consisted of procarbizine orally at a dose of 6.25 mg/kg/day for 3 days and cyclophosphamide at 50 mg/kg/day for 4 days and antithymocyte globulin at 1.25 mg/kg/day for 3 days. A conventional regimen of short course methotrexate and cyclosporin A (CSA) was used for the prophylaxis of GVHD. Engraftment (ANC > 500 X 10^6/L) was documented on day +14. The early post-BMT period was uneventful without the evidence of acute GVHD. After initial excellent graft take for 8 months, his blood counts gradually decreased to 2.8 X 10^9/L of white cells and 28 X 10^9/L of platelets. The marrow cellularity was < 10%. There was no infectious evidence including cytomegaloviral infection or acute exacerbation of hepatitis B responsible for marrow suppression. DNA finger printing, using variable-number-of-tandem-repeats (VNTR), revealed a donor engraftment. Recombinant human granulocyte macrophage-colony stimulating factor (GM-CSF) at 5 μg/kg/day was tried for three weeks to no avail. After obtaining informed consents from both donor and recipient, we proceeded to allogeneic transplantation with PBPC mobilized with G-CSF. The donor received filgrastim at a dose of 5 μg/kg/day subcutaneously for 7 consecutive days. On day 8, the donor underwent a 7 L leukapheresis with Fenwal CS-3000 plus cell separator. The donor had no side effects during PBSC mobilization and collection.

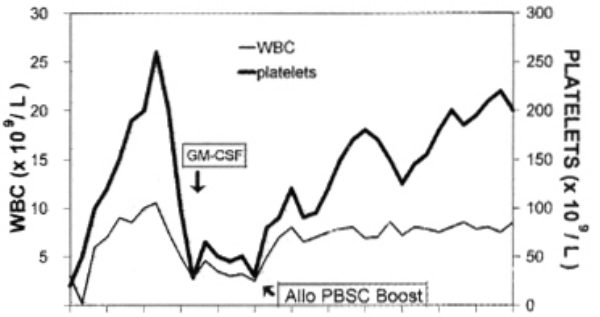

Fig. 1. Hematologic Parameters

On day 429 following BMT, a total of 1.6 X 10^8/kg mononuclear cells and 4.3 X 10^6/kg CD34+ cells was infused without further processing. Antilymphocyte globulin (10 mg/kg/day for 5 days) was used as a sole preparative therapy. As a GVHD prophylaxis, CSA was reinfused at 10 mg/kg. The patient's blood counts recovered satisfactorily after the boost (Fig. 1). Marrow aspirates on 26 days after boost showed 40% cellularity with trilineage engraftment. Full engraftment was achieved and he was monitored as

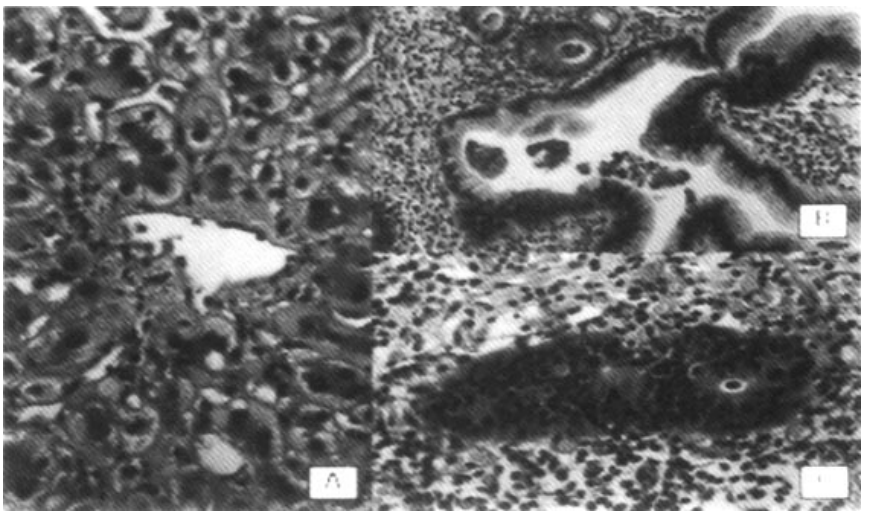

Fig. 2. Microscopic findings of GVHD of liver(A) and stomach(B, C). A. There are portal inflammatory infiltrates, bile duct damage with epithelial cell swelling and perivenular fibrosis.X400 (H&E). B,C. There are indistinct crypt abscess, apoptotic cells of mucosal glands, and dense inflammatory infiltration of lamina propria. X250, X400 (H&E)

an outpatient after discharge from hospital on day 31 after the boost.

Around 1 year after the boost (January 1995), while he was on oral CSA at 50mg, he developed abdominal pain, diarrhea and jaundice. Blood counts were normal (Hgb 12.5 g/dL, WBC 7.2 X 10^9/L, platelet 125 X 10^9/L), but liver function tests were markedly abnormal (maximum total bilirubin 19.4 mg/dL; direct bilirubin 12.4 mg/dL; alkaline phosphatase 169 IU/L; AST 54 U/L; ALT 70U/L). On the clinical ground, cytomegaloviral (CMV) enteritis and hepatitis, acute exacerbation of hepatitis B, or chronic GVHD, were suspected. CMV was excluded by negative early antigenemia assay, polymerase chain reaction and shell vial culture. A percutaneous liver biopsy and gastrofiberoscopic stomach biopsy showed the evidence of chronic GVHD (Fig. 2). No evidence of viral hepatitis was found on the liver biopsy specimen. He developed extensive chronic GVHD involving skin, eye, liver, oral and gastrointestinal mucosa. The pulse therapy of prednisolone 60 mg/day and CSA 600 mg/day resulted in gradual improvement of GVHD and he is now well on low-dose steroid at day +1055 after PBSC rescue.

DISCUSSION

Poor graft function, as indicated by a decrease in the peripheral blood counts to less than 40% of the maximal preceding values post-transplant, in association with reduced marrow cellularity, is an infrequent but serious complication of BMT[5]. Therapy of poor graft function is not always successful with a second marrow infusion or, more recently, the administration of human recombinant growth factors (CSFs). In our case, recombinant human GM-CSF at 5 μg/kg/day was tried for three weeks to no avail. As the addition of CSF-mobilized peripheral blood progenitor cells (PBPC) to autologous bone marrow grafts markedly improves hematopoietic recovery, infusion of donor-derived PBSC may also help to overcome insufficient hematopoiesis after allogeneic BMT. The first report of PBSC for allogeneic transplantation was by Kessinger et al[6]. They reported rapid tri-lineage engraftment using PBSC collected during steady-state haematopoiesis; however, a total of nine leukaphereses were required to obtain sufficient cells. Russell et al. and Dreger et al. used G-CSF mobilized PBSC for allogeneic transplantation[2, 7]. Both patients were reported to have sustained tri-lineage engraftment with good hematopoietic function.

The clinical advantages of PBSC transplants over BMT for allogeneic transplantation have been described in a number of studies. For the donor, the harvest can be performed without the need for a general anesthesia and avoids the usually minor but not negligible morbidity associated with BM harvesting[8]. Modern automated continuous flow cell separators can process 9 L of blood in 3 h without the need for central vascular catheters, providing there is good venous access. G-CSF has a high safety profile with only minor side-effects.

For the recipient, potential advantages of the use of PBSC include accelerated neutrophil and platelet engraftment as has been documented following autologous PBSCT. The high number of progenitor cells that can be harvested from G-CSF-mobilzed peripheral blood may be particularly advantageous in transplantation for aplastic anemia where an increased risk of rejection has been associated with the infusion of less than 3 X 10^8 BM cells/kg[9].

Potential disadvantages of allogeneic PBSCT include the theoretical increased risk of GVHD due to the presence of approximately 1 log larger numbers of T lymphocytes in the leukapheresis products than in BM[2-4]. Unexpectedly, however, incidence and severity of acute GVHD were not increased[10]. Data on chronic GVHD with limited follow-up periods are controversial. However, tendency toward an increased incidence of chronic GVHD has been reported in some studies, correlating with T cell doses[2, 10]. The chronic form of GVHD seemed to be less sensitive to CSA given either prophylactically or therapeutically. Improvement in the prophylaxis and control of chronic GVHD, such as the addition of steroids or a partial T cell depletion, should be considered in case the chronic GVHD in allogeneic PBSCT might affect the survival and performance adversely.

This case suggests that mobilized PBSCs are capable of providing a complete, sustained hematopoietic engraftment, and the use of primed PBSC for allogeneic transplantation is a feasible alternative to BM in treating poor graft function after BMT. Nevertheless, further studies are required to fully assess its pros and cons, particulary in terms of GVHD and survival.

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