Successful allogeneic marrow transplantation from donors with hematologic malignancies

YENER KOÇ¹, BAŞAK OYAN¹, MOHAMMED S. AKHTAR², DAVID P. SCHENKEIN², KENNETH B. MILLER²

¹Hacettepe University Faculty of Medicine, Department of Medical Oncology, Ankara-Turkey, ²Tufts University, New England Medical Center, Department of Hematology and BMT Unit, Boston, MA-USA

ABSTRACT

We report two patients with leukemia who underwent successful allogeneic marrow transplantation from donors with hematologic malignancies. A patient with acute myeloid leukemia underwent allogeneic bone marrow transplantation procedure from his HLA-compatible sibling, who had chronic lymphocytic leukemia. Similarly, another patient with chronic myeloid leukemia underwent allogeneic transplantation from his HLA-matched sister, who had a past history of Hodgkin’s disease. Both recipients continue to do well at +92 and +80 months, respectively. Both patients have normal trilineage hematopoiesis without any signs of donor-related malignancies at present. [Turk J Cancer 2004;34(3):118-121]

KEY WORDS:
Allogeneic, transplantation, malignancy, donor

INTRODUCTION

Allogeneic transplantation remains the only curative treatment modality for certain hematologic disorders. While allogeneic marrow transplantation is the treatment of choice for chronic myeloid leukemia and aplastic anemia, it has become an increasingly important treatment strategy in the management of various other disorders, including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphoid leukemia (CLL), myelodysplasia, sickle cell disease, thalassemia, as well as severe congenital immunodeficiency states (1-5). However the major limiting factor in bone marrow transplantation (BMT) is the availability of an HLA-matched sibling. After an extensive search, only about 30% of the potential recipients will have an HLA-matched sibling available (5). The presence of a hematologic malignancy in marrow donors leads to their exclusion from the donation process, thus further limiting this valuable donor pool. Here, we report successful marrow transplantations from two donors with hematologic malignancies.

CASE REPORT

Case 1

A 56 year old Caucasian male presented in June 1990 with low grade fever, arthralgia and profuse sweating. An extensive work-up for rheumatology and infectious diseases
was unrevealing. In August 94, he developed symptomatic anemia, requiring red cell transfusions. In Feb 1995, a bone marrow biopsy revealed hypercellular marrow with increased reticulin fibrosis, and was consistent with myelodysplastic syndrome (MDS). Cytogenetic evaluation of the marrow revealed 46XY/47XY, +marker karyotype, with marker being a derivative of chromosome 3. In April, 95, the patient developed progressive thrombocytopenia, hypercalcemia and atrial fibrillation. A repeat marrow evaluation showed presence of more than 30% blasts, showing cytoplasmic staining for Factor VIII-related antigen and was consistent with M7 variant of acute myeloid leukemia (AML, M7).

The patient underwent induction chemotherapy consisting of cytarabine and idarubicin, followed by an allogeneic BMT from his HLA-matched brother. The 56-year-old male donor, though completely asymptomatic, was found to have peripheral lymphocytosis. Pre-transplant evaluation revealed a white cell count of 17.9x10^9/L, hemoglobin of 13.7 g/dl, hematocrit 42.1%, platelet count 255x10^9/L, and absolute lymphocyte count of 7.6x10^9/L. Peripheral blood smear showed numerous smudge cells. Flow cytometric analysis of the peripheral blood revealed co-expression of CD5/CD20 antigens on 92% of the circulating B-lymphocytes. Physical examination was negative for lymphadenopathy or hepatosplenomegaly. The donor was diagnosed to have Stage 0 CLL, based on the clinical and immunophenotypic evaluation outlined above.

After obtaining an informed consent from the recipient, bone marrow transplantation was performed on June 15, 1995 following conditioning with cyclophosphamide (60 mg/kg, days -5, -4), etoposide (30 mg/kg, day -4) and TBI (1200 cGy total). Cyclosporine-A, which was used to prevent both graft rejection and GVHD, was started 1 day before allograft as an intravenous infusion at a dose of 2.5 mg/kg/day and the dose was adjusted according to the serum level of cyclosporine-A (target level: 450-550 ng/ml). Subsequently, patient received oral cyclosporine-A 5 mg/kg per day in 2 divided doses starting on post-transplantation day 50. Methotrexate was administered as a part of GVHD prophylaxis at a dose of 15 mg/m^2 intravenously on day 1 and 10 mg/m^2 on day 3 after the allograft. Early post-transplant course was complicated by grade IV mucositis and grade I acute graft versus host disease (GVHD). The patient also developed extensive chronic GVHD involving skin, oral mucosa, peripheral nerves and the lungs, which was responsive to a combination of prednisone, cyclosporine and azathioprine. In the setting of a clinical trial, colchicine was added to help control lung GVHD, and was associated with a good clinical response.

The recipient continues to do well with a follow-up of more than 92 months following the transplant procedure. His most current peripheral blood counts showed a white cell count of 7.1x10^9/L, hemoglobin 12.5 g/dl, hematocrit 38.8, platelet 19x10^9/L and absolute lymphocyte count of 0.816x10^9/L, with normal morphology, and without any evidence of CLL by flow-cytometric evaluation.

**Case 2**

A 26-year-old Caucasian male was diagnosed in November 1991, with Philadelphia chromosome positive chronic myeloid leukemia (CML). After cyto reduction with hydroxyurea, the patient underwent an allogeneic BMT from his HLA-matched sister on March 26, 1992 following a conditioning regimen consisting of cyclophosphamide and TBI. Post transplantation course was uncomplicated, without any evidence of GVHD. His donor’s history was remarkable for Hodgkin’s disease (HD) diagnosed in 1982. Following a staging laparotomy and splenectomy, she was determined to have Stage IIA disease and was successfully treated with mantle-field radiotherapy.

The patient did well until November 1994, when he relapsed with chronic phase CML, marked by an additional chromosomal abnormality, monosomy 7 at the time of relapse. The patient was treated with donor lymphocyte infusions (DLI), which led to a clinical and molecular remission, as determined by PCR study of peripheral blood for bcr/abl translocation. Subsequently the patient developed severe right hip and ankle pain in October 1995. MRI study showed a mass lesion involving the S1 vertebral body with expansion into the pelvis. Needle biopsy of the mass was consistent with chloroma that was managed with local radiation with resolution of pain.

In January 1996, the patient developed pancytopenia and recurrent bone pains. Bone marrow evaluation revealed 57% blasts, consistent with blastic phase of CML. He underwent induction chemotherapy with cytarabine and idarubicin, followed by a second allogeneic transplantation (April 1996) using peripheral stem cells from the same donor. Conditioning regimen consisted of busulfan (16 mg/kg total), cyclophosphamide (60 mg/kg, days -5, -4) and etoposide (30 mg/kg, day -4). GVHD prophylaxis...
consisted of cyclosporine-A and short-term methotrexate at the same doses and schedule as the previous patient. Post-transplant course was complicated by grade IV mucositis, grade I acute GVHD, and limited chronic GVHD involving skin and gastrointestinal tract. The patient discontinued cyclosporine in October 96 and was started on interferon with the hope to prevent recurrence.

The donor was in remission from her HD at the time of marrow as well as peripheral stem cell donation, as determined by clinical and radiological criteria. The recipient continues to do well after a follow-up of +80 months following the second transplant. His most current laboratory evaluation showed a white cell count of $4.9 \times 10^9/L$, Hemoglobin of 13.0 g/dl, hematocrit of 39.6%, and platelet count of $160 \times 10^9/L$, with normal morphology, and without any clinical or laboratory evidence of either CML or HD. Repeated studies on peripheral blood for bcr-abl translocation by polymerase chain reaction (PCR) technique have been negative. He has also been followed by chest radiographs at 6-month intervals that have all been normal.

**DISCUSSION**

Marrow transplantation from HLA-matched siblings, compared to matched unrelated transplants carries a reduced morbidity and mortality. However, only about one third of the potential recipients have an HLA-matched sibling available (5). Any malignant process that has been diagnosed in the donor leads to exclusion from the marrow/stem cell donation process, thus further limiting this valuable donor pool for their siblings requiring an allogeneic BMT for curative purposes.

We report two cases in which donors have had hematologic malignancies. One of the donors had early CLL, while the other had history of HD in remission at the time of donation. The recipient continues to show normal hematopoiesis and without any evidence of donor-related malignancies after a follow-up of +31 and +21 months, respectively.

This is the first report in the literature of allogeneic transplantation procedure being performed from donors with hematologic malignancies. Each of the recipients had only one sibling with a perfect HLA-match. Other potential options for acquisition of appropriate marrow for these recipients would have been: HLA-mismatched sibling marrow, matched-unrelated marrow (MUD), or cord blood. Although allogeneic transplantation from these alternative donor sources would have been feasible, this would carry an increased morbidity and mortality for their recipients (6).

There is no information in the literature as to the risks incurred by the transplant recipients if the donors have had hematologic malignancies. It is theoretically possible for clonal disorders of the donors to be transmitted to the recipients via marrow or stem cell infusion. Engraftment of these donor-related malignant clones may occur in the recipients, thus putting them at risk for developing donor-related malignancies.

As far as volunteer donors are concerned, only normal individuals are allowed to donate marrow under the auspices of the National Marrow Donor Program, with health requirements similar to those applied to blood donors (7). As per the published guidelines for volunteer donors from World Marrow Donor Association, only pregnancy and HIV/HTLV positivity are listed as absolute reasons for exclusion from the donation process (8). In these guidelines, there are no specific instructions available regarding the donors, who have hematologic disorders including malignancies. We have to bear in mind that these guidelines that are meant for the volunteer donors may not be directly applicable to matched sibling donor transplants.

In both of our cases, the risks as well as benefits of different treatment strategies were explained in detail to the patients, who opted for HLA-matched sibling transplantation. After obtaining informed consents, we decided to proceed with the transplantation procedure.

While both CLL and HD are clonal disorders, they are not known to involve the pluripotent stem cells. The stem cells from the donor with early CLL engrafted normally, leading to trilineage hematopoiesis, while clones of malignant cells did not engraft and selectively eliminated in the recipient. In experimental models, it is extremely difficult to obtain populations of proliferating leukemic cells in CLL. In case of allogeneic bone marrow transplantation, the recipients are severely immune suppressed following conditioning regimens, resembling to but less immune suppressed than SCID mice. Peripheral blood and bone marrow cells from patients at all stages of CLL was shown to engraft in SCID mice at low levels (9). However, although the SCID microenvironment was permissive for the maintenance of CLL cells, it did not enhance the proliferation (9). To enhance proliferation of CLL cells, cytokines were
administered. However, treatment with IL-2 alone or in combination with IL-7 failed to enhance the level of CLL engraftment in SCID mice. The lack of proliferation of leukemic cells in the donor may be explained by lack of stromal cell support.

Stromal cells are known to promote proliferation and differentiation of B-lymphocytes (10,11). IL-7 is absolutely required for marrow B lymphopoiesis and stromal cells are the only cells in the marrow that produce IL-7 (12). Both stromal cell contact and IL-7 are essential for B-lymphopoiesis. However, many stromal cell lines mediate early proliferative stages of B lymphopoiesis, and fail to support differentiation beyond the pre-B cell stage. The differentiation of pro-B cells to the pre-B cell stage occurs when IL-7 is removed from the cultures (13,14). Therefore, IL-7 negatively regulates B-cell differentiation by maintaining cells in a proliferative, pro-B cell state, independent of stromal cells. Stromal cells regulate B lymphopoiesis by limiting the amount of IL-7 available to the developing precursors. The regulation of the availability of IL-7 also minimizes any inhibitory effects that IL-7 possesses. Differentiation of pre-B cells into more mature B cells can not occur in the presence of stromal cells and relatively high level of IL-7 (T-46). However, differentiation can proceed when the exogenous IL-7 is removed. So, the concentration of IL-7 is highly important. Therefore, by limiting the availability of IL-7, stromal cells may limit the amount of proliferation that a precursor undergoes, allowing each cell the chance to further differentiate into a more mature B cell.

In the light of the findings summarized above, B-lymphopoiesis is highly regulated and stromal cell contact and a strict regulation of IL-7 concentration should exist. These findings explain the reason for the selective normal hematopoietic engraftment in the patient receiving the marrow graft contaminated with CLL cells.

With the more widespread use of allogeneic transplantation procedure, similar situations in which donors carry a diagnosis of hematologic malignancy are bound to arise in the future. While caution is still advised, it seems that the patients with early CLL and HD in-remission for more than a decade could be effective donors for the management of poor-risk leukemias requiring allogeneic transplantation for curative purposes.

References