ALLOGENEIC PERIPHERAL BLOOD STEM CELL TRANSPLANTATION IN A PATIENT WITH ACUTE MYELOCYTIC LEUKEMIA: FIRST EXPERIENCE OF ERCIYES UNIVERSITY

Akut myelositer lösemili bir hastada allojenik periferik kök hücre transplantasyonu: Erciyes Üniversitesinin ilk deneyimi

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Özet: *Allojenik hemopoetik kök hücre nakli, akut myelositer lösemi (AML) tedavisinde en etkili tedavi modalitesidir. Bu makalede Erciyes Üniversitesi Tıp Fakültesi'nde ilk defa HLA tam uygun kardeşinden kemik iliği nakli yapılan bir AML vakası literatür ışığında sunulmuştur.*

Anahtar Kelimeler: *Akut myelositer lösemi, Allojenik periferik kök hücre nakli, Kemik iliği*

Abstract: *Allogeneic bone marrow transplantation is the most effective treatment modality for the therapy of acute myelocytic leukemia (AML). A patient with AML has undergone allogeneic peripheral blood stem cell transplantation from his HLA full-matched brother which constituted the firstexperience of Erciyes University Medical Faculty, Department of Hematology, Bone Marrow Transplantation Unit. The case was discussed under the light of relevant literature.*

Key Words: *Leukemia, Myelocytic, acute; Transplantation, Homologous; Bone marrow; Hemopoietic stem cell transplantation*

The field of bone marrow transplantation (BMT) has been widely extended in the last 30 years following the demonstration, in the 1970s, that treatment with very high dose of radio-chemotherapy combined with allogeneic BMT could produce cure in patients with poor risk leukemia (1,2).

The concept of curative therapy in BMT rest on two factors. Firstly, hematological rescue with either allogeneic, syngeneic or autologous stem cells avoids the lethal consequences of bone marrow damage and thus allows the administration of very high doses of effective antitumor agents. Secondly, if the immune system of the transplanted marrow is capable of exerting an antitumor effect, then marrow transplantation may also be effective as a form of adoptive immunotherapy (3,4). This second phenomena is only observed in allogeneic BMT for hematological malignancies (graft-versus leukemia or lymphoma effect: GVLE).

Over the last two decades, the therapy of patients with acute myeloid leukemia (AML) has improved considerably and steadily. Between 65 to 85 % of adult patients achieve complete remission (CR) with current chemotherapy combinations (5). Thereafter, there are three major therapeutic options: further courses of chemotherapy, autografting and allografting. Conventional therapy for AML results in 20-35% disease free survival (DFS) after five years and the overall survival (OS) of patients with de novo AML is still only 9-19 months (5-7). Autologous BMT produces 30-50 % five year DFS and offers an alternative to conventional chemotherapy or to allogeneic BMT in patients over 40 or those in second remission (8). Allogeneic

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BMT in first CR produces a 50-65 % probability of cure and is the treatment of choice for patients under 40 (Age is an important risk factor and in patients over 40 years, the survival rate is reduced to approximately 20-30 %) (9).

We present a case of an allogeneic stem cell transplantation to an AML patient in complete remission from his HLA full matched brother performed for the first time in Erciyes University Medical Faculty, Department of Hematology, Bone Marrow Transplantation Unit.

CASE REPORT

A twenty year-old male patient complaining of easy fatigue, weakness, palpitation, nose and gingival bleeding was admitted to Erciyes University Medical Faculty Hematology Department in April 1999. His medical history was unremarkable . Physical examination revealed a blood pressure of 110/70 mm Hg, pulse rate 88/minute and no abnormality in systemic examination except pallor of skin and mucosa. Laboratory examination showed Hb: 8.1 g/dl, WBC: 13300/mm3 and in peripheral smear myeloblastic cells 50%, granulocytes 20% and lymphocytes 30% were detected. Bone marrow aspiration revealed hypercellular marrow which was infiltrated with myeloblastic cells (FAB-M2) and there was depression in normal myeloid and erithroid cells. Bone marrow was PAS(-), Naphtol Acetate Esterase (-) and Sudan Black (+). Flow cytometry showed CD 13(+), CD 33(+) panmyeloid staining. The patient was diagnosed as AML- M2.

After cytarabin-daonurubicine induction chemotherapy bone marrow aspiration revealed complete hematologic remission. Intermediate dose ara-C (500 mg/m2/12 hours for 3 days) and idarubicine (10 mg/m2 for 3 days) consolidation treatment was administered twice.

General characteristics of transplantation treatment protocol, prognostic evaluation and survival rate were explained to both patient and his family. Informed consent was obtained from the patient.

All hematologic, biochemical, bacteriologic, virologic and immunologic tests of the patient and donor were performed. No pathology that could have been obstacle to transplantation was detected.

Hickman catheter was inserted by Cardiovascular Surgery. Condition regimen consisted of Busulfan (1mg/kg/6 hours p.o. –8,-7,-6,-5 days for 4 days) and cyclophosphamide (60 mg/kg/day at –4, -3 days for 2 days). Cytoprotective mesna therapy was administered as equivalent doses of cyclophosphamide. The donor was admitted to the hospital at 5th day. Hematopoetic growth factor (granulocyte colony stimulating factor) 10g/kg/day was administered for stem cell mobilization. Stem cell apheresis was done at –1 and 0 days. 5,6 x 108 mononuclear cells (6,2 x 106/kg CD34(+) stem cells) were harvested after two apheresis.

Allogeneic stem cells were infused from intra-atrial catheter on day 0. Blood group of patient was 0Rh (-) and the donor group was 0Rh (+). After stem cell infusion, Anti-D immunoglobulin was administered because of Rh incompatibility. Antibacterial (ciprofloxacin 500 mg twice day p.o.), antiviral (acyclovir 200 mg 5 times a day p.o.) and anti protozoal (trimethoprim-sulfametaxasole 160 mg-180 mg 3 times per day p.o.) prophylaxis were done. For prophylaxis of GvHD immunosuppresive treatment (methotrexate 15 mg/m2/i.v. on +1, +3, +6 days and cyclosporine 5-10 mg/kg p.o. or i.v. beginning from day –1 until + 180th day) was given. For prophylaxis of GvHD and CMV infection, all blood products was irradiated (2500 cGy) and the leukocytes were depleted by special filters. Febrile neutropenia developed on the 7th day. Physical examination and cultures were negative. Fever was kept under control with empirical antibiotic treatment (meropenem 3x1 gr/day/i.v.). On 17th day leukocyte engraftment (WBC > 0.5x109/L) and on 18th day platelet engraftment (platelet > 20x109/L) were observed. Grade I GvHD was observed in the patient. An increase in liver function tests was detected (AST 506 IU/dl, ALT 404 IU/dl, total bilirubin/direct bilirubin 0.9/0.2). This increment in liver function tests led us to contemplate isolated

liver GVHD but liver biopsy was not performed because of low platelet count (20-30x109/L). Prednisolon 2mg/kg/day was started. Liver function tests began to improve on 2nd day of corticosteroid treatment and therapy was ceased by decreasing the dose step by step. Antiprotozoal and immunosuppressive therapy was continued until 100th day. Bone marrow aspiration performed on 100th day was normocellular. The patient's blood group was 40% ORh(+) on 40th day and 80% ORh(+) 0n 100th day. The patient was still in complete hematologic remission on day 120.

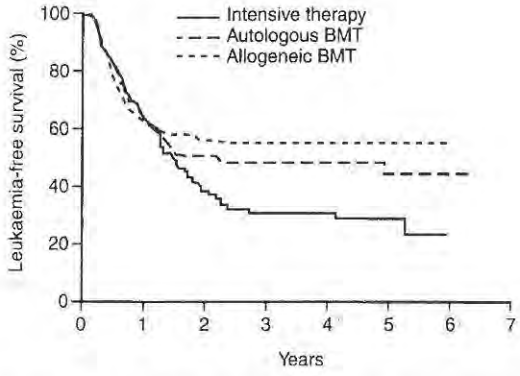

Figure 1. Comparison of the three different therapeutic strategies. Adapted from (6).

DISCUSSION

AML has an untreated survival of weeks to months, and patients at presentation may have multiple complications from cytopenias (infections, bleedings) or leukemic cell burden (leucostasis, leptomeningeal disease). Therefore, induction chemotherapy is generally initiated semiemergently. Thus, the treatment of AML has two goals: 1) induction of a CR and 2) postremission therapy to prolong remission and prevent relapse by using either further chemotherapy or BMT [allogeneic, autologous or syngeneic] (5,10,11). However, initial induction treatment may achieve high CR between 60 and 75 % of adults with de novo AML; without further chemotherapy, the median time to relapse for first remission patient is commonly less than one year (5). Both relapse and long term survival probabilities can be considerably improved with additional postremission therapies (10). The selection of most appropriate post-remission therapy for an individual patient depends on detailed knowledge of their prognostic factors (principally age and cytogenetics) and the availability of suitable donor. Prospective comparisons of the different approaches are difficult, since only patients with a suitable donor are candidates for allogeneic transplantation and clear evidence of benefit with this approach exists (3). Recently, peripheral stem cell transplantation (PSCT) has been used instead of bone marrow as a source of progenitor cell. Not only did PSCT terminate the risk of anesthesia and pain for donor, but it caused early engraftment and discharge period for recipient as well.

Allogeneic stem cell transplantation (SCT) is a well established therapy for patients with AML, and has been proven to be superior to chemotherapy and autologous transplants in first CR patients (6). The success of allogeneic SCT has been limited by transplantation related mortality. Graft versus host disease (GvHD) alone or in combination with infections or interstitial pneumonia account for a substantial proportion of failures following allogeneic SCT (12). A dramatic reduction of transplant mortality has been reported in Europe over the past decade and this is making allogeneic transplantation more attractive when compared to other forms of therapy (1). Better prevention of acute GvHD is one of the reasons of improved outcome, and in particular the widely used combination of cyclosporin and methotrexate full dose (13).

The three different strategies were compared in a randomized controlled trial of 623 adults in CR after induction treatment (6). Projected DFS at 4 years was higher in the allogeneic BMT group (55%), compared with autologous BMT (48%) and intensive postremission chemotherapy (30%) (Figure 1).

Soccie et al analyzed the International Bone Marrow Transplantation Registry of 6691 patients (2058 AML) who were free of their original disease for at least two years (14). Among patients who underwent transplantation for AML, the relative mortality rate was 19.2 % (95 percent confidence interval, 12.7 to 25.7) two years after transplantation ; and 10.2 % (95 percent confidence interval 7.0 to 13.4) five years after transplantation; it decreased to 4.5 % (95 percent confidence interval, 1.0 to 8.0) nine years after transplantation. In patients who receive an allogeneic BMT as treatment for AML who are free of their original disease two years later, the disease is probably cured. However, for many years after transplantation, the mortality among these patients is higher than that in a normal population.

In conclusion; allogeneic BMT provides long term survival in patients with AML, provides the best post remission therapy and is never inferior in outcome to autologous BMT or chemotherapy. However , newer strategies to improve the efficacy and reduce the morbidity of allogeneic BMT should devised.

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