



Haploidentical Transplantation Experience in Turgut Ozal Medical Center: Case Report and a Review of Literature

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Abstract

Haploidentical hematopoietic stem-cell transplantation is an optional transplant modality for patients without a Human Leukocyte Antigen-matched donor. Still, one-third of patients who might benefit from allogeneic transplantation are able to find a Human Leukocyte Antigen-matched related donor. In need of immediate stem-cell transplantation, haploidentical donor is an important solution for many patients. Previously, haploidentical hematopoietic stem-cell transplantation was characterized by a high rejection rate, graft-versus-host disease, graft failure, and transplant-related mortality, but there have since been significant improvements in some areas. Development of new extensive T-cell depletion methods with megadose stem cell administration have overcome problems of haploidentical hematopoietic stem-cell transplantation. We presented an applied case haploidentical hematopoietic stem-cell transplantation as an experience in Turgut Ozal Medical Center.

Key Words: Haploidentical; Transplantation; Experience.

Turgut Özal Tıp Merkezi'ndeki Haploidentik Nakil Deneyimimiz: Olgu Sunumu ve Literatür Sunumu

Özet

Haploidentik kök hücre nakli HLA uyumlu donörü olmayan hastalar için başka bir alternatif nakil modelidir. Hala, allojenik nakil gereksinimi olan hastaların ancak üçte biri HLA uyumlu vericiye sahiptir. Acil kök hücre nakli gereksiniminde haploidentik nakil bir çok hasta için önemli bir çözüm yoludur. Daha önceleri haploidentik hematopoetik kök hücre nakli yüksek oranda graft rejeksiyonu, graft versus host hastalığı, graft başarısızlığı ve nakil ile ilgili mortalite ile karakterize idi, fakat T hücre depleksiyonundaki yeni gelişmeler ve mega doz kök hücre nakli yönetimi haploidentik kök hücre naklinde bazı problemlere çözüm oldu. Biz bir vakaya uygulanan Turgut Özal Tıp Merkezi'ndeki haploidentik kök hücre nakli deneyimimizi sunduk.

Anahtar Kelimeler: Haploidentik; Nakil; Deneyim.

INTRODUCTION

The possibility of using a family donor sharing only one haplotype with a recipient affected by haematological malignancy has been investigated for many years because it would permit a donor in every case for every patient. Haploidentical haematopoietic stem-cell transplantation (HSCT) is an alternative transplant modality for patients without a Human Leukocyte Antigen (HLA)-matched donor. Previously, haploidentical HSCT was characterized by a high rejection rate, graft-versus-host disease (GVHD), graft failure, and transplant-related mortality, but there have been significant improvements in some areas since then (1). Development of new extensive T-cell depletion methods with megadose stem cell administration have overcome problems of haploidentical HSCT such as graft failure, but increased relapse rate and prolonged immune deficiency remain as unresolved problems of T-cell depletion (2,3).

Patients with relapsed or refractory acute lymphoblastic leukaemia (ALL) have poor prognosis. In these cases,

allogeneic stem cell transplantation after reinduction therapy is a common way of treating the patients (4). This paper presents a case of haploidentical HSCT treated at Turgut Ozal Medical Center, Turkey, in the context of the relevant literature.

CASE REPORT

A 26-year-old, previously healthy woman presented in 2012 with a three-week history of fatigue and jaundice. She previously had been diagnosed with B-cell ALL-L2 in 2005 and was treated with 8 cycles of Hyper-CVAD chemotherapy: Course A consisting of cyclophosphamide, vincristine, doxorubicin (also known as Adriamycin), and dexamethasone on cycles 1-3-5-7; and Course B of methotrexate and cytarabine on cycles 2-4-6-8. The patient had no history of blood transfusion or exposure to drugs or poisons. There was no family history for any particular diseases. On admission, she was well oriented and her body temperature was 36°C, pulse rate was 92 bpm, and respiratory rate was 15/min. The skin was pale and signs of petechiae were visible on her legs. No abnormal enlarged lymph nodes were palpable in any part of her body. The abdomen was not

distended. The spleen was palpable 1 cm below the left costal margin, whereas the liver was not palpable. Laboratory values were as follows: leukocyte count 16.100/microL, haemoglobin 8.8 g/dL, haematocrit 25%, mean corpuscular volume (MCV) 94.5 fL, mean corpuscular haemoglobin (MCH) 29.6 pg, mean corpuscular haemoglobin concentration (MCHC) 34.1 gm/dl, red cell distribution width (RDW) 29.5, platelet count 16.000/microL, prothrombin time 12 sec, partial thromboplastin time 25.9 sec, lactate dehydrogenase (LDH) 422 U/L, total bilirubin 0.8 mg/dl, and indirect bilirubin 0.5 mg/dl. Immunoglobulin G (IgG) direct Coombs test was negative. Peripheral blood smear revealed 70% lymphoblasts, 25% neutrophils, and 5% lymphocytes. Platelets formed small clusters and red blood cell morphology was normal. There was no other evidence of coincidental or precipitating infections. Bone marrow examination and flow cytometry examination were consistent with B-cell ALL-L2. Serologic examinations for Human Immunodeficiency Virus (HIV) and hepatitis A, B, and C were all negative. Abdominal ultrasonography was notable only for splenomegaly (splenic length was 15.5 cm). The patient was considered as a relapsed ALL case. The patient then completed six cycles of Hyper-CVAD chemotherapy. Following chemotherapy, her siblings were screened for histocompatibility but there was no matching donor; hence an unrelated volunteer donor was sought, but could not be found. Meanwhile, the patient entered a remission phase and was discharged without any visible problems. Six months later, the patient re-presented with a relapse. The patient had four sisters. Haploidentical transplantation was planned from a healthy 37-year-old, sister with a 6/10 HLA match. FLAG-IDA chemotherapy protocol was planned for induction treatment, comprising: on days 1–5, fludarabine 30 mg/m²/day IV followed by cytarabine 2 g/m²/day IV; idarubicin 10 mg/m²/day IV on days 1–3; filgrastim 5 µg/kg/day/ subcutaneous (SC) to begin on day 6 until neutrophil recovery. Two cycles of FLAG-IDA treatment were given. A subsequent bone marrow examination indicated remission. The patient received a haploidentical transplantation from her sister (6-loci HLA match). Conditioning regimen (Bu/Flu/ATG; busulfan 4×0.8mg/kg/day for 4 days [on days -6 to -2], fludarabine 30mg/m²/day for four days [on days -6 to -2], anti-thymocyte globulin 5mg/kg/day for two consecutive days [-2 and -1]) was started.

Granulocyte Colony Stimulating Factor (G-CSF) 10 µg/kg/day/SC treatment was started with the donor for five days (starting from day-4 according to the patient's protocol). Using a Spectra Optia device, 79×10⁶ CD34 (+) stem cells/kg were harvested from the healthy donor and were processed for selection of 99.2% of T-and B-lymphocytes via the Tübingen method (day 0 of Bu/Flu/ATG regimen). A total of 59×10⁶ CD34 (+) stem cells/kg were harvested and given to the patient on the same day without any complication. Allogeneic stem cell transplantation was applied successfully. Subsequently, the patient experienced no fever or infection. She only used prophylactic antimicrobials and required no additional antimicrobial

therapy. Cyclosporine (2×1.5 mg/kg/day I.V) and methotrexate (for four days: 15 mg/m² on day 1; and 10 mg/m² on days 3, 6 and 11) were initiated as a treatment for GVHD prophylaxis. Four units of platelet suspension obtained by apheresis were given as supportive therapy. Neutrophil engraftment occurred on the 14th day of transplantation, and platelet engraftment occurred on the 17th day. The patient was discharged successfully on the 19th day of transplantation.

DISCUSSION

Allogeneic stem cell transplantation is recommended for high-risk patients as well as for those with acute lymphoblastic leukaemia who relapse (4). Our case was first diagnosed in 2005 and subsequently relapsed twice, in 2011 and 2012. When first diagnosed in 2005, allogeneic stem cell transplantation was not considered because she had no positive indications of poor prognosis such as t(9;22), t(4;11), t(1;19), or 11q23. The patient was therefore evaluated as being within the standard risk group (Table 1).

Table 1. Risk stratification of adult ALL

Feature	Standard	High Risk
Age, Cytogenetics	<35 year	≥35 year Ph/BCR-ABL+ t(4;11)/ALL1-AF4 t(1;19)/E2A-PBX 11q23+
Leukocyte count	≤30.000/ µL (B origin) ≤100.000/ µL (T origin)	>30.000/ µL (B origin) >100.000/ µL (T origin)
Immunophenotype	Thymic T-ALL	Pro B-ALL Early T-ALL Mature T-ALL
Complete response time After induction	≤4 week <%0.01	>4weeks ≥%0.01

The patient first relapsed in 2011. Allogeneic stem cell transplantation is recommended for relapsed ALL (5). In our case, allogeneic stem cell transplantation was planned after the first relapse; however, the patient had no HLA-identical donor either within her family or the Turkish Marrow Donor Programme. There was also no appropriate umbilical cord blood in the Turkish Cord Blood Bank Network.

We considered performing haploidentical HSCT after the second relapse, because her disease status did not allow us to search or wait for appropriate donors. We therefore selected the patient's sister as an alternative donor, as she had a haplotype-identical, four loci-mismatch HLA phenotype (Table 2).

The patient received a haploidentical transplantation from her sister (6-loci HLA match). We did not select her mother because of her mother had only 5-loci HLA match as well as comorbid diseases.

Table 2. HLA phenotypes of patient and donor

HLA phenotype	Patient	Donor
HLA A	A*24, A*24	A*24, A*68
HLA B	B*15 B*35	B*15 B*35
HLA C	C*07, C*12	C*04, C*07
HLA DRB	DRB1*07, DRB1*11	DRB1*01, DRB1*07
HLA DQB	DQB1*03, QB1*03	DQB 1*03, DQB 1*05

Patients who are scheduled to receive an allogeneic stem cell transplant should be administered several cycles of chemotherapy in order to reduce the burden of malignant cells (4). In the first step in our case, patient was given FLAG-IDA chemotherapy protocol for induction treatment. After two cycles of FLAG-IDA chemotherapy, bone marrow examination indicated complete remission. G-CSF treatment at a dose of 10 µg/kg/day/SC for five days is recommended for donor mobilization (6). It is recommended that harvested allogeneic stem cells should be administered on day-zero of the patient protocol, without being frozen. (7). In our case, the donor was a healthy 37-year-old woman whose HLA group was 6/10 compatible with the patient. G-CSF treatment was given for five days for mobilization, and 79×10⁶ /kg CD34 (+) stem cells were successfully harvested via peripheral blood via a Spectra Optia device. Initially, such transplantation was considered too toxic, but following the development of specific conditioning regimens and ex vivo T-cell depletion, its feasibility and efficacy have been demonstrated mainly for acute leukaemia (1). The donor's CD 34 (+) stem cells were treated via selection of 99.2% of T and B lymphocytes using the Tübingen method, and the patient received 59×10⁶ /kg CD34 (+) stem cells intravenously on the same day without any issues.

Complications such as GVHD, graft failure, reduced graft-versus-leukaemia effect, and delayed immune reconstitution can take place haploidentical transplantation. The GVHD rate is 80% with three or more individuals' antigen HLA-mismatched transplantation. There are several ways to prevent severe GVHD: a) elimination of reactive immune cells (T-cells) in the donor bone marrow; and b) post-transplant active immunosuppression treatment (methotrexate, cyclosporine, cyclophosphamide, and others) (8). In our patient, the donor stem cells were harvested as T-cells; B-cell elimination was applied and prophylactic immunosuppression regimen was applied, comprising cyclosporine (2×1.5 mg/kg/day intravenously), methotrexate for 4 days (days 1, 3, 6 and 11), and immunoglobulin (5 gr/once a week /intravenously) until the 100th day; thus GVHD was not observed and we did not give other immunosuppressive treatment. Graft failure following allo-HSCT is a life-threatening complication and is most commonly caused by the reactivity of recipient T-cells, natural killer cells, or antibodies against grafted haematopoietic cells of the donor. Therefore, selective drug combination regimens were commenced instead of a potent chemotherapy regimen, like melphaFlan, busulfan, thiopeta,

fludarabine, anti-thymocyte globulin, OKT-3 (muromonab-CD3) or a combination of these agents (8). We used the most up-to-date conditioning regimen in the literature, consisting of a combination of busulfan, anti-thymocyte globulin, and fludarabine. However, stem cell dose and duration of engraftment are usually associated with graft failure. CD 34 (+) stem cell > 10×10⁶ / kg should be infused for this purpose. This high dose of CD 34 (+) stem cells neutralizes recipient reactive cytotoxic T lymphocytes (8). We administered 59×10⁶ / kg CD 34 (+) (megadoses) to the patient to prevent graft failure. It should be kept in mind that delayed immune recovery is an important cause of infection-related mortality. Epstein Barr virus, Cytomegalovirus, Toxoplasma, Candida, and Aspergillus are the main causes of mortality (8). Our patient was administered antimicrobial prophylactic therapy during haploidentical HSCT. There were no signs of fever or infection during hospitalization, so she received no additional antimicrobial therapy.

All patients undergoing transplantation require blood product support in the form of red blood cell and platelet transfusions until the transplanted marrow cells engraft sufficiently to support haematopoiesis. This generally requires 14 to 21 days or more with bone marrow but is accelerated with peripheral blood progenitor cells, where engraftment typically takes place within 10 to 14 days (9). Four units of platelet suspension obtained by apheresis were given as supportive therapy to our patient, and erythrocyte suspension was not used. Neutrophil engraftment occurred on the 14th day after transplantation, and platelet engraftment occurred on the 17th day. In haploidentical-HSCT, 30-day treatment-related mortality has been reported to be around 10% (3). Our patient was discharged successfully on the 19th day of the transplantation.

In conclusion, novel management techniques like alloreactive T-cell depletion and post-transplant cell therapy are promising tools to improve immune recovery in haploidentical HSCT. Although haploidentical transplantation is still an experimental method of treatment, it is an important alternative transplantation modality in countries like Turkey, where a stem cell donor programme has not yet been established.

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