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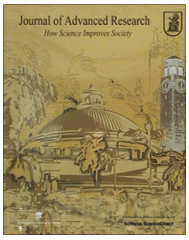

ORIGINAL ARTICLE

Allogeneic hematopoietic stem cell transplantation for non-malignant hematological disorders

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) from a geno-identical matched sibling (MSD) is one of the most successful therapies in patients with non-malignant hematological disorders. This study included 273 patients with severe aplastic anemia (SAA), 152 patients with B-Thalassemia major (BTM), 31 patients with Fanconi's anemia (FA), 20 patients with congenital immunodeficiency diseases (ID), and 13 patients with inherited metabolic disorders (IMD) allografted from a MSD. In SAA, the 8-year overall survival (OS) of the whole group patients was 74%. OS was significantly better in patients conditioned with fludarabine and cyclophosphamide (Flu/Cy) than in those who received cyclophosphamide and antithymocyte globulin (Cy/ATG) ($p = 0.021$). Acute graft-versus-host disease (aGVHD) grade II–IV occurred in 15% while chronic GVHD (cGVHD) occurred in 28%. In BTM, the 12-year disease-free survival (DFS) of the whole group of BTM patients was 72.4%. DFS was 74% for peripheral blood stem cell (PBSC) group compared to 64% in the BM stem cell group. The incidence of graft rejection was significantly lower in patients who received PBSC than in those who received BM (9% vs 25%) ($p = 0.036$). AGVHD grade II–IV and cGVHD occurred in 15% and 12% of the whole group of BTM patients respectively. In FA, the 5-year OS was 64.5%. Graft rejection occurred in 10% of patients. Grade II–IV aGVHD occurred in 16% while cGVHD occurred in 4%. In ID, the 5-year OS was 62%. Graft rejection occurred in two (10%) patients. Three patients (15%) developed grade II–IV aGVHD, 2 of them progressed

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to secondary cGVHD. In IMD, OS was 46% at 5 years. Graft rejection occurred in 8% of patients. AGVHD grade II–IV occurred in 15% while cGVHD occurred in 14%. In conclusion, Allo-HSCT provides a higher DFS rate over conventional therapies for patients with non-malignant hematological disorders with prolonged survival.

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative modality for a variety of nonmalignant disorders involving bone marrow (BM) failure and thalassemia [1]. It has been successfully used as a replacement therapy for patients with severe aplastic anemia (SAA), B-thalassemia major (BTM), Fanconi anemia (FA), immunodeficiency diseases (ID) and inherited metabolic disorders (IMD) [1,2].

SAA is characterized by profoundly hypocellular marrow with marked reduction in 2 or 3 peripheral blood parameters [3]. Allo-HSCT is a convincing treatment modality for children and young adults with SAA and best results are achieved from a matched family donor [4]. The expected 5 years OS for patients <20 years old receiving HLA identical sibling HSCT as upfront treatment is 88% and for patients aged 21–50 years 72% [5]. On the other hand, BTM is an inherited disease requiring lifelong red blood cell transfusion to treat the anemia caused by ineffective intramedullary erythropoiesis and enhanced red blood cell destruction in the peripheral circulation [6]. Prognosis is highly dependent on compliance and socio-economic status. Mortality is high due to therapy related complications especially liver fibrosis and heart disease. The best curative modality is replacement of defective marrow by allo-HSCT [7]. FA, an autosomal recessive disorder belonging to the group of chromosomal instability syndrome is characterized clinically by congenital malformations, hypersensitivity to alkylating agents, progressive marrow failure, and predisposition to acute myeloid leukemia [8]. Allo-HSCT has also been established as the only treatment modality that can restore normal hematopoiesis in these patients [1]. ID is a group of inherited disorders characterized by severe impairment of innate and adaptive immune systems, which leads to early death from infectious complications. Replacement of the defective lineage by allo-HSCT from healthy allogeneic donors remains the curative approach for most patients [9]. IMDs and osteopetrosis are a diverse group of diseases arising from genetic defects or osteoclast disorders. Onset in infancy or early childhood is typically accompanied by rapid deterioration and associated with early death. Timely diagnosis and immediate referral to a specialist with discussion of the patient by a multidisciplinary team including a transplant physician are essential steps in management of these disorders [10].

While improved supportive care has extended the life span of patients affected by these diseases, definitive cure is only achieved by allo HSCT. The careful selection of pre-transplant conditioning can significantly reduce early transplant related mortality (TRM), increase the probability of durable engraftment and leads to better survival especially when linked to an HLA identical donor.

The aim of this study was to illustrate and report the outcome of allo-HSCT in different non-malignant hematologic conditions treated at our Institute.

Patients and methods

Patient population

Between May 1997 and April 2012, a total of 489 patients with non-malignant hematological diseases were allografted at Nasser Institute for Research and Treatment, Ministry of Health, Cairo, Egypt, using different conditioning regimens. *Allo-HSCT protocols were approved by the institutional review board. Written informed consent was obtained from patients or their parents.*

Allo-HSCT

Intermediate-resolution DNA typing by polymerase chain reaction sequence specific oligonucleotides probe (PCR–SSO) for human leukocyte antigen (HLA) class I (HLA-A, -B, -C) and class-II (HLA-DRB1, -DQB1) was performed [11]. ALL donors were siblings or other family members and at least 6/6 HLA matched. PBSC Donors were injected subcutaneously with granulocyte-colony stimulating factor (G-CSF, 10 μg/kg daily for 5 days) and mobilized PBSC was collected the day of last injection. One to 2 apheresis procedures were planned by means of COBE Spectra continuous cell separator (Gambro, Lakewood, CO, USA) using Spin–Nebraska protocol [12]. For BM donors, aspirations were performed under general anesthesia from posterior ileum region. Enumeration of total WCC, MNC and CD34 +ve cells was done by flow cytometry (Coulter EPICS, Coulter electronics, Hialeah, FL, USA) using anti CD34 monoclonal antibody HPCA2 (BD, San Jose, CA, USA). The aim was to collect at least 5×10^8 mononuclear cells (MNC) and/or 3×10^6 viable CD34+ cells/kg recipient's body weight. The products of PBSC apheresis and BM harvest were infused to patients on the same day of collection (day 0).

Chimerism analysis

To assess engraftment, degree of chimerism in patients was monitored at regular intervals by Fluorescent In-situ Hybridization (FISH) XY chromosome analysis in case of sex mismatch and by PCR for variable number tandem repeats (VNTR) analysis at D+28 and D+56 post-transplant using loci Apo B, YNZ, DIS 80, 33.1, 33.4, 33.6 and H Ras [13].

Conditioning regimen

181 SAA patients received Flu/Cy regimen consisting of cyclophosphamide 50 mg/kg/day (days −5 to −2) and fludarabine 40 mg/m^2/day (days −3 to −1). Another 92 SAA patients received Cy/ATG regimen consisting of cyclophosphamide 50 mg/kg/day (days −5 to −2) and antithymocyte globulin (ATG) 10 mg/kg/day (days −5 to −3). BTM patients were