Hematopoietic Stem Cell Transplantation in β-Thalassemia Major: The Egyptian Outcome

Thesis

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Dedication

I dedicate my dissertation work

to my mother and father who gave me love,

encouragement and being always there for me.

to my sisters and many friends for their

support and encouragement.

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Abstract

Hematopoietic stem cell transplantation (HSCT) offers curative potential for β-thalassemia major. **Aim of the work:** To evaluate the thalassemia-free survival and outcome of stem cell transplantation in the Egyptian experience and to analyze the patients and donors' characteristics as well as transplantation related factors that could affect the graft success rate. **Methods:** This study retrospectively analyzed 174 patients who underwent stem cell transplantation for β-thalassemia major in Nasser institute, between January 1997 and December 2014. **Results:** Their age at the time of transplantation ranged from 0.7 to 23.7 years; with a mean of 6.1±4.2 and median 4.6 years. One hundred and six were males (60.9%) and 68 (39.1%) females (M/F ratio: 1.6). Out of the 174 patients; 38 (21.8%) were in class I, 110 (63.2%) were in class II, and 26 (14.9%) were in class III. Twenty-six (14.9%) patients received bone marrow and 148 (85.1%) received peripheral blood stem cells (PBSC) harvest. The donors were selected based on degree of human leukocyte antigen (HLA) matching, and all of them were HLA-identical donors. 153 were matched sibling donors (MSD) and 10 were matched parent donors (MPD). The study showed that the probabilities of 5-year overall survival (OS) is 74.9%, disease free survival (DFS) is 61% and transplant related mortality (TRM) is 18.4%. Graft failure occurred in 12.6%, and the use of PBSC showing lower incidence of graft failure (GF) than BM harvest. **Conclusion:** The optimum age for transplantation is from 2-6 years, PBSC harvest and higher stem doses have more favorable outcomes and stem cell source was the main risk factor of graft failure.

Keywords: HSCT, Thalassemia, OS, DFS

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List of Abbreviations

Abbreviation	Meaning
Ags	Antigens
aGVHD	Acute graft-versus-host disease
AIHA	Autoimmune hemolytic anemia
ALG	Antilymphocyte globulin
allo-HSCs	Allogeneic hematopoietic stem cells
allo-HSCT	Allogeneic hematopoietic stem cell transplantation
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ARDS	Adult respiratory distress syndrome
ATG	Anti-thymocyte globulin
auto-HSCs	Autologous hematopoietic stem cells
auto-HSCT	Autologous hematopoietic stem cell transplantation
BM	Bone marrow
BMT	Bone marrow transplantation
Bu	Busulfan
CBC	Complete blood count
cGVHD	Chronic graft-versus-host disease
CMV	Cytomegalovirus
CsA	Cyclosporine A
CTLA	Cytotoxic T lymphocyte antigen
CVD	Cardiovascular disease
CVRFs	Cardiovascular risk factors
CVS	Chorionic villus sampling
Cy	Cyclophosphamide
DAH	Diffuse alveolar hemorrhage
DAT	Direct antiglobulin test
DES	Dry eye syndrome
DFS	Disease free survival
DLI	Donor lymphocyte infusion
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
EBMT	European Group for Blood and Marrow Transplantation

EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECP	Extracorporeal photopheresis
EFS	Event free survival
FISH	Fluorescent in-situ hybridization
fL	Femtoliter
Flu	Fludarabine
FN	Febrile neutropenia
FT_4	Free thyroxine
G-CSF	Granulocyte colony-stimulating factor
GF	Graft failure
G-PBMCs	Granulocyte colony-stimulating factor mobilized peripheral blood mononuclear cells
GVHD	Graft-versus-host disease
GVL	Graft-versus-leukemia
Gy	Gray
hATG	Horse anti-thymocyte globulin
Hb	Hemoglobin
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV-Ab	Hepatitis C virus antibody
HHV	Human herpes virus
HIV	Human Immunodeficiency virus
HLA	Human leukocyte antigen
HLH	Hemophagocytic lymphohistiocytosis
HRD	Haplo-related donors
HRQL	Health-related quality of life
HSCs	Hematopoietic stem cells
HSCT	Hematopoietic stem cell transplantation
IgG	Immunoglobulin G
IL	Interleukin
IMH	Mediterranean Institute of Hematology
IPn	Interstitial pneumonia
IPS	Idiopathic pneumonia syndrome
IV	Intravenous

LDH	Lactate dehydrogenase
LIC	Liver iron concentration
M/F	Male to female
MAC	Myeloablative conditioning
MC	Mixed chimerism
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
Mel	Melphalan
MHC	Major histocompatibility complex
MMF	Mycophenolate mofetil
MPD	Matched parent donors
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MSCs	Mesenchymal stem cells
MSD	Matched sibling donors
MTX	Methotrexate
MUD	Matched unrelated donors
NMDP	National Marrow Donor Program
OS	Overall survival
PB	Peripheral blood
PBSC	Peripheral blood stem cells
PCR	Polymerase chain reaction
PCR-SSO	Polymerase chain reaction sequence specific oligonucleotides
PCs	Pulmonary complications
PERDS	Peri-engraftment respiratory distress syndrome
pg	Picogram
PO	Per os
PRES	Posterior reversible encephalopathy syndrome
PTCy	Post-transplantation Cyclophosphamide
PUVA	Psoralen combined with ultraviolet A
QALE	Quality-adjusted life expectancy
QoL	Quality of life
rATG	Rabbit anti-thymocyte globulin
RBCs	Red blood corpuscles
RDs	Related donors
RFs	Risk factors

rhG-CSF	Recombinant human granulocyte colony-stimulating factor
RIC	Reduced-intensity conditioning
RNA	Ribonucleic acid
RPLS	Reversible posterior leukoencephalopathy syndrome
RTC	Reduced-toxicity conditioning
SCs	Stem cells
SCT	Stem cell transplantation
SMR	Sexual maturity rating
SQUID	Superconducting quantum interference device
STR	Short tandem repeats
T_3	Triiodothyronine
T_4	Thyroxine
TBI	Total body irradiation
TCD	T-cell depletion
TNF	Tumor necrosis factor
tPA	Tissue plasminogen activator
TPN	Total parenteral nutrition
TRH	Thyrotropin-releasing hormone
TRM	Transplant related mortality
TSH	Thyroid stimulating hormone
UCB	Umbilical cord blood
UCBT	Umbilical cord blood transfusion
URD-HSCT	Unrelated donor hematopoietic stem cell transplantation
VNTR	Variable number tandem repeats
VOD	Veno-occlusive disease
WHO	World Health Organization

Introduction

Since the first successful transplant performed in a child with thalassemia major by Thomas and colleagues in Seattle ***(Thomas et al, 1982)***, many patients with thalassemia major have been cured by HSCT, in most cases performed using an HLA-identical sibling donor with bone marrow (BM) as the stem cell source ***(Locatelli and Stefano, 2004)***.

In recent years, the number of transplants has increased further, involving a growing number of medical centers including those of the Far and Middle East, where thalassemia is endemic and represents a serious health and socioeconomic problem ***(Li et al, 2012)***.

Several new approaches have been applied to reduce the toxicity of conditioning regimens, improve strategies for the prevention of graft-versus-host disease (GVHD), and optimize supportive care. The 5-year probabilities of overall survival and thalassemia-free survival are currently estimated as 87% to 97% and 80% to 89%, respectively ***(Angelucci and Baronciani, 2008)***.

In 1989, the stem cell transplantation (SCT) program started in Egypt on a narrow scale. In 1997, the transplant rate increased dramatically with the opening of the SCT unit at Nasser Institute. The total number of transplants performed till June 2007 was 1362; 80% of the cases were allogeneic and 20% autologous ***(Mahmoud et al, 2008)***.