Comparative study between Post-Transplant Cyclophosphamide vs Methotrexate in HLA-Matched related donor in hematological malignancies as regard Acute Graft Versus Host Disease or CytomegaloVirus reactivation

Thesis

Submitted for Partial Fulfillment
of Master Degree in **Clinical Hematology**

By

Ahmed Mohammed Elhosainy
(M.B.B.Ch)

Under Supervision of

Prof. Dr: Mohamed Mahmoud Moussa
Professor of Internal Medicine & Hematology
Faculty of Medicine, Ain Shams University

General. Dr: Essam Ali AbdElmohsen
Head of Hematology Department
Maadi Armed Forces Medical Compound
Consultant of Hematology, Military Medical Academy

Dr: Haydi Sayed Mohamed
Lecturer of Internal Medicine & Hematology
Faculty of Medicine, Ain Shams University

Faculty of Medicine, Ain Shams University
2019

سورة البقرة الآية: ٣٢

Acknowledgments

First and foremost, I feel always indebted to ***Allah*** *the Most Beneficent and Merciful.*

I would like to express my sincere appreciation and gratitude to ***Prof. Dr. Mohamed Mahmoud Moussa,*** *Professor of Internal Medicine and Clinical Hematolog, faculty of medicine, Ain Shams University, for his supervision.*

I would like also to express my sincere appreciation and gratitude to ***General Dr. Essam Ali AbdElmohsen****, Head of Hematology Department, Maadi Armed Forces Medical Compound, Consultant of Hematology, Military Medical Academy, for his continuous directions and support throughout the whole work.*

Really I can hardly find the words to express my gratitude to ***Dr. Haidy Said Mohammed,*** *Lecturer of Internal Medicine & Hematology, Faculty of Medicine, Ain Shams University for her supervision, continuous help, encouragement throughout this work and tremendous effort she has done in the meticulous revision of the whole work. I really appreciate her patience and support.*

I would like also to express my sincere appreciation and gratitude to my senior and close friend ***Colonel Dr. George Bahig Soryal, Dr. Mai Samir AbdElmawgod.***

Last but not least, I dedicate this work to my family, especially my lovely wife ***Doaa*** *whom without her sincere emotional support, pushing me forward this work would not have ever been completed.*

Ahmed Mohammed Elhosainy

List of Contents

List of Abbreviations

Abb.	Full term
aGvHD	*Acute graft-versus-host disease*
AIDS	*Acquired immune-deficiency syndrome*
AML	*Acute myeloid leukemia*
APC	*Antigen-presenting cells*
ATG	*Anti-thymocyte globulin*
BLPD	*B-cell lymph proliferative disease*
BM	*Bone marrow*
BMI	*Body mass index*
BU	*Busulphan*
CAMs	*Cell adhesion molecules*
CCI	*Charlson Comorbidity Index*
CD	*Cluster of Differentiation*
cGVHD	*Chronic graft-versus-host disease*
CLL	*Chronic lymphocytic leukemia*
CML	*Chronic myelocytic leukemia*
CMV	*Cytomegalovirus*
CRP	*C-reactive protein*
CSA	*Cyclosporine A*
CT	*Computerized tomography*
CTLs	*Cytotoxic T lymphocytes*
DMSO	*Dimethyl sulfoxide*
EBV	*Epstein–Barr virus*
ECOG	*Eastern Cooperative Oncology Group*
FHCRC	*Fred Hutchinson Cancer Research Center*
G-CSF	*Granulocyte colony-stimulating factor*
GvHD	*Graft-versus-host disease*
HL	*Hodgkin lymphoma*
HLA	*Human leucocyte antigen*

List of Abbreviations cont...

Abb.	Full term
HSCs	*Hematopoietic stem cells*
HSCT	*Hematopoietic cell transplantation*
HSCT	*Hematopoietic stem cells Transplantation*
HSCT-CI	*Hematopoietic cell transplantation-specific comorbidity index*
Ig	*Immunoglobulin*
IL	*Interleukin*
IPA	*Invasive pulmonary aspergillosis*
KPS	*Karnofsky Performance Score*
MDACC	*MD Anderson Cancer Center*
MDS	*Myelodysplasia*
MDS	*Myelodysplastic syndrome*
MM	*Multiple myeloma*
MSC	*Mesenchymal stromal cells*
MTX	*Methotrexate*
NHL	*Non Hodgkin lymphoma*
NK	*Natural killer*
NMA	*Non-myeloablative*
NRM	*Non-relapse mortality*
OS	*Overall survival*
PBSC	*Peripheral blood stem cells*
PCP	*Pneumocystis carinii pneumonia*
PCR	*Polymerase chain reaction*
PFTs	*Pulmonary function tests*
PTLD	*Post-transplantation lymphoprofilerative disorder*
RBCs	*Red blood cells*
RCTs	*Randomized controlled trials*

List of Abbreviations cont...

Abb.	Full term
RIC	*Reduced-intensity conditioning*
RSV	*Respiratory syncitial virus*
SDF1	*Stromal-derived factor 1*
SF	*Serum ferritin*
TBI	*Total body irradiation*
TCD	*T- cell depletion*
TRM	*Treatment-related mortality*
UCB	*Umbilical UCB*
US	*United States*
VCAM-1	*Vascular cell adhesion molecule-1*
VOD	*Veno-occlusive disease*
VZV	*Varicella zoster virus*

List of Tables

List of Tables cont...

List of Figures

Fig. No.	Title	Page No.

List of Figures cont...

INTRODUCTION

Graft-versus-host disease (GVHD) is a major toxicity of allogeneic hematopoietic stem cell transplantation (HSCT)**.** It is a clinicopathologic syndrome of T cell–mediated alloreactivity that leads to significant morbidity and mortality ***(Filipovich et al., 2005).*** On the other hand, removal of T cells that are responsible for GVHD has been associated with a higher rate of graft failure and relapse ***(Bashey et al., 2017).***

Many pharmacologic immunosuppressive regimens were introduced to reduce GvHD. The combination of calcineurin inhibitors (CNIs), such as tacrolimus or cyclosporine,with methotrexate remains the most common regimen used for GvHD prophylaxis ***(Kanakry et al., 2014).***

Although CNIs inhibit acute GVHD, they are not as effective in reducing the incidence of chronic GVHD, even if administered for 24 months after transplantation. Moreover, CNIs may impair immune reconstitution by inhibiting T-cell development and increasing the risk of disease relapse. Thus, patients with hematologic malignancies undergoing allo-BMT might benefit from GVHD prophylaxis that would minimize the use of CNIs, prevent GVHD, and retain a graft-versus-tumor effect ***(Baron et al., 2014).***

Cyclophosphamide was one of the first agents shown to be effective in controlling acute GVHD in animal models.

Subsequent mouse studies demonstrated that tolerance to minor histocompatibility antigens could be induced if Cyclophosphamide was given in a high dose 2 to 3 days after alloantigen exposure ***(Zhao et al., 2008).***

Variety of clinical trials using high-dose post-transplantation Cyclophosphamide (PTCy) in HLA-matched and haplo-identical donors, mostly in the adult population shown to be effective as well ***(Kanakry et al., 2014; O'Donnell et al., 2014).***

PTCy targets alloreactive donor T cells that are highly proliferative early after BMT, thus minimizing the risk of severe GvHD, while still enabling survival of resting memory T cells that can offer protection against infection and against tumor relapse ***(Luznik et al., 2016).***

Cyclophosphamide can safely be administered in high doses after alloBMT because of its favorable safety profile, including lack of toxicity to primitive hematopoietic stem cells ***(Peccatori et al., 2014).***

These promising clinical trials using PTCy have demonstrated the safety and feasibility of PTCy as sole of GvHD prophylaxis after myeloablative HLA-matched T cell replete BMT in adults, with rates of GvHD similar to that of HLA-matched BMT with conventional immunosuppression, including a CNI and Methotrexate***(Cieri et al., 2015).***

AIM OF THE WORK

The aim of the work is to assess safety and efficacy of using Cyclophosphamide as GvHD prophylaxis in allogeneic stem cell transplant and its effect on acute GvHD and CMV reactivation in comparison to CNIs with Methotrexate.

Chapter I

HEMATOPOIETIC STEM CELL TRANSPLANTATION

Hematopoietic stem cell transplant (HSCT) was started more than half a century ago; it is a standard treatment for many hematological malignancies. It is now established as a standard therapeutic modality for a variety of malignant and non-malignant diseases, it has evolved since from experimental bone marrow transplantation for rare cases with refractory acute leukemia, combined immune deficiency, or aplastic anemia to standard of care for patients with many congenital or acquired severe disorders of the hematopoietic system ***(Gratwohl et al., 2013).***

It is noted that the first successful allogeneic HSCT was done with bone marrow (BM) as the source of hematopoietic stem cells in 1968. In the subsequent 2 decades only bone marrow was used as the source of stem cells for transplantation. In the 1960s, experiments have shown that peripheral blood contains a small number of stem cells, which can be enriched by pre-treatment with certain chemotherapeutic drugs and hematopoietic growth factors. Therefore mobilized peripheral blood stem cells (PBSC) became another stem cell source for HSCT and PBSC has been increasingly used as it has certain advantages compared with BM. In 1978, cord blood (CB) was found to be a rich source of stem cells and was later