Evaluation of the efficacy of Thalidomide as Maintenance Therapy after Autologous Peripheral Blood Stem Cell Transplantation for Patients with Multiple Myeloma

Thesis
Submitted for fulfillment for
Master Degree of Internal Medicine

By

Hisham Mahmoud Eissa
(M.B., B.Ch.)

Supervisors

Prof. Dr. Omar Abd-Elrahman Fahmy
Professor of Internal Medicine
Faculty of Medicine
Cairo University

Dr. Mohamed Abdel-Mooti Mohamed
Assistant Professor of Medical Oncology
National Cancer Institute
Cairo University

Faculty of Medicine
Cairo University
2009

ACKNOWLEDGEMENT

All praise to Allah the All Mighty Who has provided us with knowledge and the ability to see right from wrong.

I wanted to thank my family, namely my parents for their endless support, inspiration and for simply being always there for me whenever I needed them, and my wife and kids for their support, tolerance and the care and love they have been providing to me.

I would like also to express my appreciation and respect to Prof. Dr. Omar Abd-Elrahman Fahmy, Professor of Internal Medicine, Faculty of Medicine, Cairo University, for his guidance, encouragement and teaching he has been providing to me since I started working within our BMT Unit in Nasser Institute under his supervision.

Needless to express how deeply thankful I am to Dr. Mohamed Abdel-Mooti Mohamed, Assistant Professor of Medical Oncology, NCI, Cairo University, for his true and sincere assistance he has provided to me in preparing and working on this thesis.

Moreover, I would like to express my extreme respect and appreciation for Prof. Dr. Hossam Kamel, President of Cairo University and Head of our Hematology and BMT Unit in Nasser Institute, and Prof. Dr. Alaa Elhaddad, Vice Dean of NCI and Head of BMT Unit in NCI, Cairo University, for all the support and sincere mentorship they have been providing to me since I joined their team, and for the true career and learning opportunities they have helped me through with extreme good will and assistance. I am extremely proud to say that I have worked with such professional and knowledgeable professors.

Special thanks goes to all my colleagues and staff members in Hematology and BMT Unit in Nasser Institute, without whom, this work would not have even been done, and for their extreme sincerity in serving patients and providing the best medical service they can. Special thanks and appreciation goes to my dear friend and senior Dr. Mohamed El-Emary for the invaluable friendship and assistance he has provided to me.

Abstract

Purpose: The aim of the present study was to compare the outcome of the multiple myeloma (MM) patients who underwent autologous stem cell transplant (ASCT) and received post-ASCT maintenance thalidomide, to those who didn't.

Patients and Methods: Thirty-two MM patients in partial remission (PR), very good partial remission (VGPR), or in complete remission (CR), underwent ASCT receiving high dose melphalan 200 mg/m^2 divided on 2 days. Peripheral blood stem cells (PBSC) were used as stem cell rescue. Thirteen of them were given thalidomide maintenance treatment on full hematopoietic recovery (neutrophil>1000, platelets>100,000) in a dose of 100 mg po daily for 1 year, in a non-randomized fashion. Nineteen patients didn't receive any maintenance treatment after ASCT and were only put under follow-up.

Results: Thalidomide (n=13) and non-thalidomide arms (n=19) were almost comparable in virtue of patient characteristics criteria. The mean times to neutrophil and platelets recovery were 11.3 and 13.4 respectively. There was no transplant-related mortality faced in our study and the toxicities faced in both arms during and after transplant were not life threatening, grades 1 to 3. Peripheral neuropathy and constipation were only reported in the thalidomide arm and no deep venous thrombosis events were reported in neither of both arms. At a median follow up of 33.3 months, the overall survival (OS) in the thalidomide arm was 76.9% versus 84.2% in the non-thalidomide arm, but the difference did not reach statistical difference ($p = 0.661$). The progression-free survival (PFS) in the thalidomide arm was 76.9%, versus 78.9% for the non-thalidomide arm, again the difference was also statistically insignificant ($p = 0.906$).

Conclusion: High dose melphalan was found to be a well tolerated HDT with minimal side effects, and post transplant thalidomide maintenance therapy was found to be a safe protocol with non life-threatening toxicities. However, the OS and PFS of both groups of the study did not show statistical difference. Larger numbers of patients need to be recruited, randomized trials are needed, and better pre-transplant prognostic categorization of the patients needs to be offered as part of pre-transplant assessment.

Key Words: Multiple myeloma, high dose chemotherapy, bone marrow transplantation, autologous peripheral blood stem cell transplantation, thalidomide.

Table of Contents

List of Abbreviations

ABMT: Autologous Bone Marrow Transplantation.
ABMTR: American Bone Marrow Transplant Registry.
ACD: Acid Citrate Dextrose.
AL: Amyloid.
ALL: Acute Lymphoblastic Leukemia.
AlloSCT: Allogenic Stem Cell Transplantation.
AML: Acute Myeloid Leukemia.
APBSCT: Autologous Peripheral Blood Stem Cell Transplant.
ASCO: American Society of Clinical Oncology.
ASCT: Autologous Stem Cell Transplant.
B2m: Beta-2 microglobulin.
BJP: Bence - Jones protein.
BM: Bone Marrow.
BMD: Bone Marrow Density.
BMT: Bone Marrow Transplantation.
Bu: Busulfan.
CC: Conventional Chemotherapy.
CFU-GM: Granulocyte-Macrophage Colony Forming Unit.
cGVHD: Chronic Graft Versus Host Disease.
CBC: Complete Blood Count.
CMV: Cytomegalovirus.
CNS: Central Nervous System.
CR: Complete Remission.
CRP: C - reactive protein.
CSF: Cerebrospinal Fluid.
CSF: Colony Stimulating Factor.
DFS: Disease-Free Survival.
DLI: Donor Lymphocyte Infusion.
DNA: Deoxyribonucleic acid.
DMSO: Dimethylsulfoxide.
DVT: Deep Venous Thrombosis.
EBMT: European Group for Blood and Marrow Transplantation.
ECOG: Eastern Co-operative Oncology Group.
EFS: Event-Free Survival.
ELISA: Enzyme-Linked ImmunoSorbent Assay.
ESR: Erythrocyte Sedimentation Rate.
FGF: Fibroblast growth factors.
FISH: Flowcytometry In Situ Hybridization.
FLC: Free Light Chain.
GC: Germinal Center.
G-CSF: Granulocyte Colony Stimulating Factor.
GM-CSF: Granulocyte Macrophage Colony Stimulating Factor.
GVHD: Graft Versus Host Disease.

GVM: Graft versus Myeloma.
HBc ab: Hepatitis B core antibody.
HBe ag: Hepatitis B e antigen.
HBs ag: Hepatitis B surface antigen.
HCV: Hepatitis C Virus.
HD: Hodgkin Disease.
HDT: High Dose Therapy.
HGF: hematopoietic Growth Factor.
HHV: Human Herpes Virus.
HSCT: Hematopoietic Stem Cell Transplantation.
IBMTR: International Bone Marrow Transplant Registry.
IFN: Interferon.
IFM: Intergroupe Francophone du Myelome.
Ig: Immunoglobulin.
IGF: Insulin Growth Factor.
IL: Interleukin.
IP: Interstitial Pneumonitis.
IMWG: International Myeloma Working Group.
ISS: International Staging System.
KSHV: Kaposi-sarcoma Herpes Virus.
LDH: Lactate Dehydrogenase.
LMWH: Low Molecular Weight Heparin.
MDS: Myelodysplastic Syndrome.
MDT: Melphalan-Dexamethasone-Thalidomide.
MGUS: Monoclonal Gammopathy of Undetermined Significance.
MIP: Macrophage Inflammatory Protein.
MM: Multiple Myeloma.
MP: Melphalan-Prednisone.
MPT: Melphalan-Prednisone-Thalidomide.
MR: Minimal Response.
MRC: Medical Research Council.
NHL: Non Hodgkin Lymphoma.
OAF: Osteoclasts Activating Factor.
OPG: Osteoprotogerin.
ORF: Open Reading Frame.
OS: Overall Survival.
PB: Peripheral Blood.
PBS: Phosphate Buffer Saline.
PBSC: Peripheral Blood Stem Cell.
PBSCT: Peripheral Blood Stem Cell Transplant.
PCL: Plasma Cell Leukemia.
PCLI: Plasma Cell Labeling Index.
PCR: Polymerase Chain Reaction.
PET: Positron emission tomography.
PFS: Progression Free Survival.

PR: Partial Remission.
RANKL: Receptor Activation of NF-KB Ligand.
RBCs: Red Blood Cells.
RIC: Reduced Intensity Chemotherapy.
R-MP: Revlimid-Melphalan-Prednisone.
RR: Response Rate.
RT-PCR: Reverse Transcriptase Polymerase Chain Reaction.
SCF: Stem Cell Factor.
SCID: Severe Combined Immunodeficiency.
SMM: Smoldering Multiple Myeloma.
SPEP: Serum Protein Electrophoresis.
SWOG: Southwest Oncology Group.
TBI: Total Body Irradiation.
TD: Thalidomide-Dexamethasone.
Thal-DD: Thalidomide- Pegylated Liposomal Doxorubicin- Dexamethasone.
TLC: Total Leucocytic Count.
TNC: Total Neutrophil Count.
TNF: Tumor Necrosis Factor.
TRM: Transplant-Related Mortality.
VAD: Vincristine-Adriamycin-Dexamethasone.
VEGF: Vascular Endothelial Growth Factor.
VGPR: Very Good Partial Remission.
VMP: Velcade-Melphalan-Prednisone.
VOD: Veno-Occlusive Disease.
WBCs: White Blood Cells.
WHO: World Health Organization.

List of Tables

Page

List of Figures

Page

Introduction and Aim of Work

Multiple myeloma is a plasma cell neoplasm that is characterized by skeletal destruction, renal failure, anemia and hypercalcemia ***(Kyle and Rajkumar, 2004).*** The most common symptoms on presentation are fatigue, bone pains and recurrent infections ***(Kyle et al, 2003).***

The median length of survival after diagnosis is approximately 3 years. Factors that denoted adverse outcome were identified such as increase in the plasma cell labeling index, increased levels of serum beta 2-microglobulin, hypoalbuminemia, and plasmablastic features in the bone marrow and circulating plasma cells ***(Rajkumar et al, 1999).*** Recent advances have identified new prognostic markers such as the complete deletion of chromosome 13 or its long arm as detected by karyotyping, the t (4; 14) or t (14; 16) translocations and increased density of bone marrow microvessels ***(Avet-Loiseau, 2002)***.

Although myeloma remains an incurable disease, yet all patients under the age of 60 years should be considered for high dose chemotherapy with ASCT as consolidation after initial treatment. ASCT improves the likelihood of complete response, prolongs DFS and OS and is considered a major advance in myeloma therapy ***(Blade et al, 2003).*** The TRM is less than 5 percent and approximately 50 percent of the patients can be treated as outpatients. Whether or not a complete remission is achieved is an important predictor of the eventual outcome ***(Moreau et al, 2002).*** A single ASCT after induction regimens typically produces CR in about 20-40 percent of patients, with a median PFS in the range of 2.5-4 years and OS of 4-5 years ***(Barlogie et al, 2004).*** Strategies to further improve these results are directed to improve the pretransplant chemotherapy; melphalan 200 mg/m^2 being considered the standard chemotherapy as preparation protocol

(Harousseau and Attal, 2003). Also, several trials have evaluated the impact of thalidomide given as maintenance therapy after ASCT. Results of the IFM99-02 trial showed that in patients with standard prognosis, maintenance treatment with thalidomide significantly prolongs EFS ***(Harousseau et al, 2004).***

Aim of the work:

The aim of this retrospective study is to assess:

1. The outcome of ASCT in multiple myeloma patients regarding response rate (RR), disease-free survival (DFS) and overall survival (OS).
2. The influence of addition of post-transplant maintenance therapy by thalidomide to patients regarding:
    a. RR, DFS and OS.
    b. Adverse effects of thalidomide therapy.

Multiple myeloma

Definition:

The term "Multiple Myeloma" means multiple tumors in the marrow. This term was used as multiple myeloma patients usually develop numerous tumors in the bones that are detected as osteolytic lesions ***(Barlogie et al, 2001).***

Multiple myeloma is a B cell malignancy of neoplastic plasma cells that generally produce a monoclonal immunoglobulin. It accounts for around 1 percent of all malignancies and 10 percent of hematological ones. It is usually a disease of the elderly with a median age of 65 years, although it is occasionally encountered in the second decade of life ***(Barlogie et al, 2001).***

Multiple myeloma belongs to a spectrum of disorders called "plasma cell dyscrasias" that includes ***(Barlogie et al, 2001)***:

1. Clinically benign conditions such as essential monoclonal gammopathy.
2. Rare disorders such as Castleman disease and alpha-heavy-chain disease.
3. Macroglobulinemia.
4. Solitary plasmacytoma.
5. Plasma cell myeloma.

They all share plasma cell morphologic features and most are associated with the production of immunoglobulin molecules. Most of them have a monoclonal origin with resultant monoclonal protein secretion; some of them are accompanied by oligoclonal or polyclonal protein abnormalities such as Castleman disease or angioimmunoblastic lymphoproliferative disease that's now recognized as a T- cell lymphoma ***(Barlogie et al, 2001).***

Etiology and pathogenesis:

Animal models:

Plasmacytoma or myeloma can be induced in BALB/c mice by pristane oil, or even develop spontaneously in some mouse strains ***(Radl et al, 1988).*** This progresses to an autonomously growing plasmacytoma with uncontrolled expression of c-MYC due to its gene rearrangement. Generally, these plasmacytomas secrete monoclonal immunoglobulin of the IgA isotype ***(Baird, 2001)***.

Human myeloma cell lines can survive and disseminate in mice with severe combined immunodeficiency (SCID) ***(Feo-Zuppardi et al, 1992)***, thus myeloma cells from untreated patients were implanted in these models successfully providing the SCID-hu model as an in vivo read out system to study human myeloma biology. Tumor self renewal capacity can be examined in relation to maturation stage and the contribution of host accessory cells and cytokines to disease manifestations and progression elucidated. It was anticipated that new treatment principles aiming, for example, at inactivating the marrow microenvironment like biphosphonates ***(Aparicio et al, 1998)*** or targeting neoangiogenesis like thalidomide can be evaluated ***(Singhal et al, 1997)***.

Environmental exposure:

Radiation and exposure to chemicals were found to be associated with higher risks of incidence of plasma cell myeloma. Studies of atomic bomb survivors observed this fact 15 to 20 years after irradiation. On the contrary, no solid

association has been established until now between myeloma and certain infections or autoimmune diseases ***(Riedel and Pottern, 1992)*.**

Human Herpes Virus, HHV-8, also called Kaposi–sarcoma herpes virus (KSHV), already shown to be involved in the pathogenesis of Castleman disease, Kaposi sarcoma and pleural cavity lymphoma, has shown to be present in marrow dendritic cells of the majority of myeloma patients ***(Said et al, 1996)***. Some groups confirmed its presence ***(Raje et al, 1999)***, but others failed to identify it in dendritic cells generated from mobilized peripheral blood stem cells ***(Tarte et al, 1998)***.

Also no serologic evidence of HHV-8 infection was demonstrated. Nested PCR proved that 60 percent of 30 myeloma samples were positive which was faced by the fact that 44 percent of 25 normal controls showed ORF 26 sequence (one of the viral genome regions) amplification. Other viral genome regions were uniformly negative in myeloma and control samples. The proposed pathogenic mechanism for HHV-8 in myeloma, postulates that tumorigenesis occurs secondary to infection of a normal cell lineage (dendritic cells) exerting to tumor cell survival and growth promoting signals ***(Tisdale et al, 1998)***.

Genetic alterations and their role:

Multiple myeloma is a plasmablast/plasma cell tumor of germinal and post germinal center B cell origin. Germinal center B cells uniquely modify their DNA through sequential rounds of somatic hypermutation and antigen selection, and also by immunoglobulin heavy chain (IgH) switch recombination. Post GC B-cells can generate plasmablasts that have successfully completed somatic hypermutation and Ig H switching before migrating to the bone marrow, where