The Incidence of CMV Viraemia in Severe Aplastic Anemia Patients with Acute GVHD after Allogeneic Peripheral Blood Stem Cell Transplantation

Thesis

Submitted to faculty of medicine, Ain Shams University for partial fulfilment of master degree in Clinical Haematology

By

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2016

سورة البقرة الآية: ٣٢

Acknowledgments

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

My most sincere gratitude is also extended to **Prof. Dr / Mohammed Osman Azzazi,** *Professor of Internal Medicine- Clinical Haematology and BMT, Faculty of Medicine, Ain Shams University, for his enthusiastic help, continuous supervision, guidance and support throughout this work. I really have the honor to complete this work under his supervision.*

Words fail to express my appreciation to **Prof. Dr / Mohamed Mahmoud Moussa,** *Professor of Internal Medicine- Clinical Haematology and BMT, Faculty of Medicine, Ain Shams University, for his great help, valuable suggestions and directions throughout the whole work.*

I would like also to thank with all gratitude **Dr / Raafat Mohamed Abdel-fatah,** *Consultant of Medical Oncology- Clinical Haematology and BMT, National Cancer Institute, Cairo University, for the efforts and time he has devoted to accomplish this work.*

Last but not least, I can't forget to thank all members of my Family, especially my ***parents****, my* ***Husband*** *and my* ***kid*** *for pushing me forward in every step in the journey of my life.*

Mahmoud Elsayed Metwally

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List of Abbreviations

Abbr.	Full-term
aGVHD	Acute graft versus host disease
ASCT	Autologus stem cell transplantation
AuHSCT	Autologus stem cell transplantation
BAL	Bronchoalveolar lavage
BM	Bone marrow
Bu	Busulphan
cGVHD	Chronic graft versus host disease
IST	Immunosuppressive therapy
CR	Complete remission
NMDP	National Marrow Doner Program
CIBMTR	Center for International Blood and Marrow Transplantation Research
ARC	Absolute Reticulocyte Count
ALC	Absolute Lymphocyte Count
CRm	molecular CR
CSA	Cyclosporin A
Cy	Cyclophosphamide
DAH	Diffuse alveolar haemorrhage
DIC	Disseminated intravascular coagulation
PRCA	Pure Red Cell Aplasia
EBMT	European Bone Marrow Transplant
ES	Engrafment syndrome
FDP	Fibrin degradation products
Flu	Fludarabine
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte macrophage colony stimulating factor
GVHD	Graft versus host disease
GVL	Graft versus leukemia
SAA	Severe Aplastic Anemia
CMV	Cytomegalovirus
allo-SCT	

HSCT	Allogeneic stem cell transplantation
IFIs	Hematopoietic stem cell transplantation
AML	Invasive fungal infections
MDS	Acute Myeloid Leukemia
MDS/MPN	Myelodysplastic syndrome
MHA	myelodysplastic/myeloproliferative neoplasm
MPFC	Microangiopathic haemolytic anemia
MPO	multiparametric flow cytometry
MRD	Myeloperoxidase
MSD	Minimal residual disease
NCCN	matched sibiling donor
NK	National Comprehensive Cancer Network
NMA	Natural killer
PNH	Non myeloablative
ATG	Paroxysmal Nocturnal Hemoglobinemia
NSE	Antithymocyte Globulin
PAS	nonspecific esterase
PB	periodic acid-Schiff
PBSC	Peripheral blood
PCP	Peripheral blood stem cell
PI	Pneumocystitis pneumonia
PR	Prognostic index
RIC	Peripheral blood
SOS	Reduced intensity conditioning
TBI	Sinusoidal obstruction syndrome
TMA	Total body irradiation
TNC	Thrombotic microangiopathy
UCB	Total nucleated count
URD	Unrelated Cord blood
VOD	Unrelated donor
VZV	veno-occlusive disease
WBC	Varicella zoster virus
WHO	White blood count
	World Health Organization

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Abstract

Background: Aplastic anemia (AA) is defined as pancytopenia with a hypocellular bone marrow in the absence of abnormal infiltration or increased reticulin. **Aim of the Work:** This retrospective study evaluates the incidence of CMV viraemia in severe aplastic anemia patients who developed acute GVHD after allogeneic SCT in the time period from 2010 to 2015 regarding: The correlation between acute GVHD and the incidence of CMV CMV-related mortality. Disease-free survival (DFS). Overall survival (OS). **Patients and Methods:** Patients with severe aplastic anemia (SAA) who underwent allogeneic peripheral blood stem cell transplantation (PBSCT) at Nasser institute, in the time period between 2010 and 2015 (5years) were included in the study. Results: In this study 28 patients (27.18 %) developed aGVHD and 11 patients (10.6 %) developed CMV viremia. 6 patients with aGVHD developed CMV viremia (P-value=0.03). **Conclusion:** In conclusion the use of CMV prophylaxis routinely with new agents with lower toxicity, especially in patients at high risk of CMV replication, might reduce the incidence of CMV replications, reducing so the morbidity and mortality, and according to some studies may also reduce the incidence of aGVHD and its related morbidity and mortality. **Recommendations:** Further studies are needed to the relationship between CMV and acute GVHD.

Key words: aplastic anemia, CMV, GVHD, pancytopenia

Introduction

Aplastic anemia (AA) is defined as pancytopenia with a hypocellular bone marrow in the absence of abnormal infiltration or increased reticulin. AA can be inherited or acquired. AA is classified as non-severe, severe (SAA) and very severe based on the degree of the peripheral blood cytopenias. Bone marrow transplantation is the treatment of choice for young patients (age of <40 years) with SAA who have a histocompatible (HLA)-matched donor ***(Young et al., 2006)***.

Despite progress in immunosuppressive and antiviral therapy, acute graft-versus-host disease (aGVHD) and cytomegalovirus (CMV) infection remain important complications after allogeneic stem cell transplantation (allo-SCT) ***(Boeckh et al., 2009)***.

Multiple studies have shown a pathogenetic association between CMV replication and aGVHD. GVHD and its treatment put patients at risk for CMV replication. On the other hand, CMV may also play a role in the development of GVHD. CMV-infected endothelial cells have been shown to produce inflammatory cytokines such as interleukin 6. These inflammatory responses in patients after allo-SCT with CMV replication could thereby contribute to the initiation of aGVHD ***(Larsson t al., 2004; Cantoni et al., 2010).***

The most common clinical manifestations of CMV disease in allo-SCT recipients are pneumonitis, hepatitis and gastroenteritis. The introduction of prophylactic or preemptive antiviral drug treatment during this early post transplantation period resulted in a marked reducton of the incidence of CMV pneumonia ***(Ljungman, 2008)***.

The most important risk factors for CMV disease after allogeneic SCT are the serologic status of the donor and recipient. CMV-seronegative patients receiving stem cells from a CMV-seronegative donor (D−/R-) have a very low risk of primary infection if CMV safe blood products are used. Other risk factors for CMV infection include the use of high-dose corticosteroids, T-cell depletion, acute and chronic GVHD, the use of antithymocyte globulin, conditioning regimens containing fludarabine, high CMV viral load, and the use of mismatched or unrelated donors ***(Walker et al., 2007; Mori and Kato, 2010)***.

The serologic determination of CMV-specific antibodies (IgG and IgM) is important for determining a patient's risk for CMV infection after transplantation but cannot be used for the diagnosis of CMV infection or disease. Polymerase chain reaction (PCR) is the most sensitive method for detecting CMV. Quantitative PCR (qPCR) relies on the amplification and quantitative

measurement of CMV DNA, while at the same time maintaining high specificity. High levels of DNA in blood is a good predictor of CMV disease in HSCT recipients ***(Boeckh et al., 2003).***

Aim of the Work

This retrospective study evaluates the incidence of CMV viraemia in severe aplastic anemia patients who developed acute GVHD after allogeneic SCT in the time period from 2010 to 2015 regarding:

- The correlation between acute GVHD and the incidence of CMV
- CMV-related mortality.
- Disease-free survival (DFS).
- Overall survival (OS)