

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

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لَسْبَدَانِكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

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List of Contents

<i>Subject</i>	<i>Page No.</i>
List of Abbreviations	i
List of Tables.....	iii
List of Figures	v
Introduction	1
Aim of the Work.....	4
Review of Literature	
Severe Aplastic Anemia.....	5
Allogeneic Hematopoietic Stem Cell Transplantation in SAA	33
Patients and Methods.....	95
Results.....	110
Discussion	124
Summary & Conclusion	129
References	130
Arabic Summary	—

List of Abbreviations

<i>Abbr.</i>	<i>Full-term</i>
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	Engraftment syndrome
FDP	Fibrin degradation products
Flu	Fludarabine
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte macrophage colony stimulating factor
GVHD	
GVL	Graft versus host disease
SAA	Graft versus leukemia
CMV	Severe Aplastic Anemia
allo-SCT	Cytomegalovirus

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 sibling 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

List of Tables

<i>Table No.</i>	<i>Title</i>	<i>Page No.</i>
Table (1):	Some drugs and Chemicals associated with aplastic anemia	18
Table (2):	Causes of pancytopenia	20
Table (3):	Classification of aplastic anemia:	21
Table (4):	Summary of investigations required for the diagnosis of SAA.....	25
Table (5):	Criteria of aplastic anemia.....	25
Table (6):	Severe aplastic anemia.....	26
Table (7):	Very severe AA	26
Table (8):	Staging of aGvHD:	55
Table (9):	Grade of aGvHD Degree of organ involvement	55
Table (10):	Demographic data distribution of the study group.	110
Table (11):	C.O. Death distribution of the study group. ..	111
Table (12):	Alive Death distribution of the study group. .	112
Table (13):	AGVHD distribution of the study group.	113
Table (14):	CMV IgG pre BMT distribution of the study group.	114
Table (15):	CMV IgM pre BMT distribution of the study group.	115
Table (16):	CMV PCR post BMT distribution of the study group.	116

Table (17): Relation between AGVHD and CMV viremia post BMT.....	117
Table (18): DFS and OS distribution of the study group.	118
Table (19): Kaplan-Meier showing DFS according to AGVHD (2/4).	119
Table (20): Kaplan-Meier showing OFS according to AGVHD (2/4).	120
Table (21): Kaplan-Meier showing DFS according to CMV PCR post BMT.....	121
Table (22): Kaplan-Meier showing OS according to CMV PCR post BMT.....	122
Table (23): AGVHD and CMV viremia post BMT.	123

List of Figures

<i>Figure No.</i>	<i>Title</i>	<i>Page No.</i>
Figure (1):	Pathophysiology of acquired aplastic anemia.....	6
Figure (2):	Venn diagram of the clinical and pathophysiologic relationships among the bone marrow failure syndromes, leukemia, and autoimmune diseases.....	23
Figure (3):	Pie chart gender distribution of the study group.....	110
Figure (4):	Pie chart alive distribution of the study group.....	112
Figure (5):	Pie chart AGVHD/ 2-4 distribution of the study group.....	113
Figure (6):	Pie chart CMV IgG pre BMT distribution of the study group.	114
Figure (7):	Pie chart CMV IgM pre BMT distribution of the study group.....	115
Figure (8):	Pie chart CMV PCR post BMT distribution of the study group.....	116
Figure (9):	Relation between AGVHD and CMV viremia post BMT.	117
Figure (10):	DFS and OS distribution of the study group.	118
Figure (11):	Kaplan-Meier showing DFS according to AGVHD (2/4).....	119

Figure (12): Kaplan-Meier showing OFS according to AGVHD (2/4).....	120
Figure (13): Kaplan-Meier showing DFS according to CMV PCR post BMT	121
Figure (14): Kaplan-Meier showing OS according to CMV PCR post BMT	122
Figure (15): AGVHD and CMV viremia post BMT	123

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

*A*plastic 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 et 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 reduction 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)