Impact of CMV Viremia on Allogeneic Peripheral Blood Stem Cell Transplantation in Patients with Acute Leukemia

Thesis

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To:

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for their endless love, support,

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List of Abbreviations

Abb.	Full term
6-MP	*6 mercaptopurine*
ADCC	*Antibody-dependent cell-mediated cytotoxicity*
ALL	*Acute lymphoblastic leukemia*
AML	*Acute myeloid leukemia*
APCs	*Antigen Presenting Cells*
APL	*Acute promyelocytic leukemia*
ATG	*Anti Thymocyte Globulin*
AYA	*Adolescent and young adults*
BAL	*Bronco alveolar lavage*
BM	*Bone Marrow*
CART	*Chimeric Antigen Receptors-T*
CB	*Cord Blood*
CBF	*Core binding factor*
CMV	*cytomegalovirus*
CN	*Cytogenetic Normal*
CNIs	*Calcineurin inhibitors*
CR	*Complete remission*
CRS	*Cytokine release syndrome*
CSF	*Cerebrospinal Fluid*
CTLs	*Cytotoxic T-lymphocytes*
DAH	*Diffuse alveolar haemorrhage*
DLI	*Donor Lymphocyte Infusion*
DLT	*Dose Limiting toxicity*
EBV	*Epstein-Barr virus*
EC_{50}	*Half maximal effective concentration*
EFS	*Event Free Survival*
ES	*Engraftment Syndrome*
FAB	*French-American-British*

List of Abbreviations cont...

Abb.	Full term
FEV1	*Forced Expiratory Volume in 1second*
FRβ	*Folate Receptor family β*
GAVE	*Gastric antral vascular ectasia*
G-CSF	*Granulocyte colony-stimulating factor*
GF	*Graft failure*
GVHD	*Graft-versus-Host Disease*
GVT	*Graft-versus-Tumor*
HC	*Hemorrhagic cystitis*
HCC	*Hepatocellular Carcinoma*
HLA	*Human leukocyte antigen*
HSCT	*Hematopoietic stem cell transplantation*
HSV	*Herpes simplex virus*
ITD	*Internal Tandem Duplication*
MMAF	*Microtubule-disrupting agent monomethyl auristatin F*
MMF	*Mycophenolate mofetil*
MRD	*Minimal Residual disease*
NCCN	*National Comprehensive Cancer Network*
NHL	*Non-Hodgkin lymphoma*
NK	*Natural killer*
OS	*Overall survival*
PBD	*Pyrrolobenzodiazepine*
PBSC	*Peripheral blood stem cells*
PCR	*Polymerase chain reaction*
PGFR	*Platelet derived growth factor*
PI3K	*Phosphoinositide 3-kinase*
PLTD	*Post-transplant lymphoproliferative disorders*
RAF	*Rapidly Accelerated Fibrosarcoma*

List of Abbreviations cont...

Abb.	Full term
RCTs	*Randomized controlled studies*
RFS	*Relapse Free survival*
RIC	*Reduced intensity conditioning*
SOS	*sinusoidal obstructive syndrome*
SWOG	*Southwest Oncology Group*
TBI	*Total body irradiation*
TCD	*T-cell depletion*
TK	*Tyrosine kinase*
TMA	*Thrombotic microangiopathy*
TMP/SMX	*Trimethoprim-sulfamethoxazol*
TNF	*Tumor necrosis factor*
TRM	*Treatment related mortality*
TSH	*Thyroid-stimulating hormone*
VGFR	*Vascular endothelial growth factor*
VOD	*Veno-occlusive disease*
VSLI	*Vincristine sulfate liposomes injection*

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is now established as a standard therapeutic modality for a variety of malignant and non-malignant diseases. The first successful allogeneic HSCT was done with bone marrow (BM) as the source of hematopoietic stem cells in 1968.

Nowadays transplant physicians are faced with 3 viable choices of stem cells for allogeneic HSCT, namely BM, PBSC and CB and clinicians have to face the challenges of selecting the optimal stem cell source. Although all 3 sources of stem cells are capable of reconstituting the hematopoietic system in recipient after transplant, they have many inherent differences in cellular constituents and biological and immunological properties ***(Cheuk et al., 2013).***

G-CSF-mobilized PBSC are increasingly used instead of BM cells for allogeneic transplantation because they provide faster engraftment and better survival in recipients with poor-risk disease ***(Group SCTC, 2005).***

Important difference among the sources of stem cell is the amount of mature T cells present. PBSC usually contains a lot more mature T cells compared to BM, which in turn contains more T cells compared to CB, and this partly explains the differences in the risk of graft rejection and graft-versus-host disease (GVHD). Depletion of T cells is associated with

increased risk of graft rejection and disease relapse, but lower risk of GVHD ***(Switzer et al., 2014).***

One of the main reasons for preferring PSC worldwide is the important advantages provided by this method to the donor. These advantages are avoidance of anesthesia, lack of the need for hospitalization or blood transfusion, and very low serious adverse event risk ***(Sirinoglu-Demiriz et al., 2012).***

Most of the randomized controlled trials (RCTs) comparing matched related donor BM and PBSC transplantation for patients with hematological malignancies found no significant differences between the two stem cell source in important outcomes including overall survival, disease-free survival, transplant-related mortality, relapse, acute GVHD and chronic GVHD. However, all trials showed significantly faster neutrophil engraftment in PBSC transplants, and all but one trial showed significantly faster platelet engraftment in PBSC transplants, which may result in earlier hospital discharge for PBSC recipients and lower cost for PBSC transplantation. Lymphocyte recovery was also found to be better in the PBSC group in one trial ***(Powles et al., 2000)***.

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 pathogenic 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).***