Association of CD34 Positive Cell Count with Chronic Graft Versus Host Disease in patients with Acute Myeloid Leukemia who had Allogeneic Peripheral Blood Stem Cell Transplantation

Thesis

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By

Nermeen Mamdouh Salah Amin

M.B., B.Ch.

Supervised by

Prof. Dr / Hoda Ahmed Elsayed Gad Allah

Professor of Internal Medicine- Clinical Haematology and BMT
Faculty of Medicine, Ain Shams University

Prof. Dr / Mohamed Abdel-Mooti Mohamed Samra

Professor Of Medical Oncology-Clinical Haematology and BMT
National Cancer Institute, Cairo University

Assistant Prof. Dr / Walaa Ali El Salakawy

Assistant Professor of Internal Medicine- Clinical Haematology and BMT
Faculty of Medicine, Ain Shams University

Faculty of medicine
Ain Shams University
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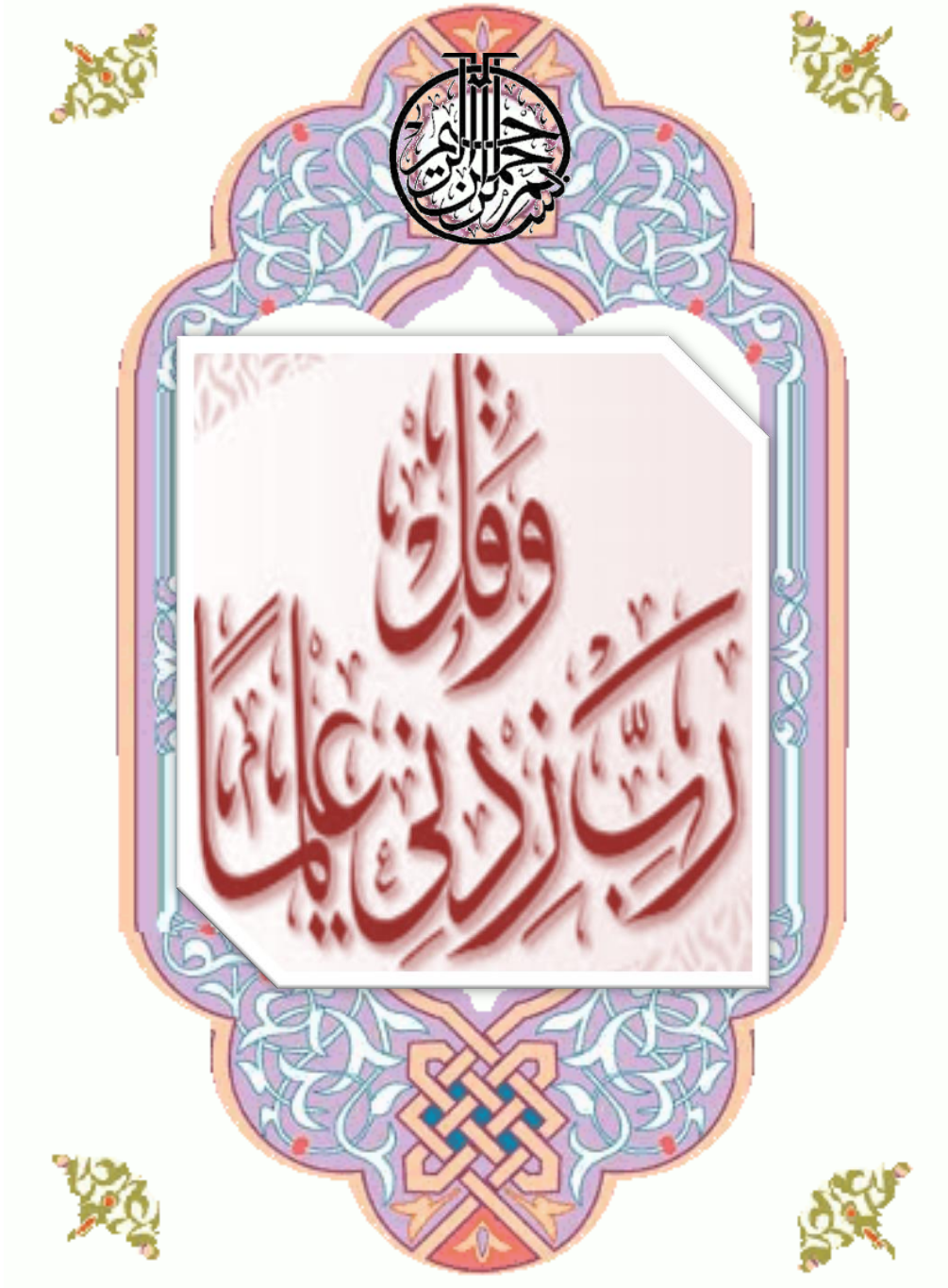
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Nermeen Mamdouh Salah Amin

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LIST OF ABBREVIATIONS

Abb.		Full Term
aGVHD	:	Acute graft versus host disease
ALLO-HSCT	:	allogenic hemopoietic stem cell transplantation
AML	:	Acute Myeloid Leukemia
APL	:	Acute promyelocytic Leukemia
ASCT	:	Autologous stem cell transplantation
ATO	:	Arsenic trioxide
ATRA	:	All trans retinoic acid
BAL	:	Bronchoalveolar lavage
BM	:	Bone Marrow
BOS	:	Bronchiolitis obliterans
Bu	:	Busulfan
CB	:	Cord blood
CD	:	cluster of differentiation
cGVHD	:	Chronic Graft Versus host disease
CIBMTR	:	Center for International Blood and Marrow Transplant Research
CR	:	complete remission
CRc	:	cytogenetic remission
CRm	:	molecular CR
CSA	:	Cyclosporine
CY	:	Cyclophosphamide
DIC	:	Disseminated intravascular coagulation
EBMT	:	Europian Bone Marrow Transplant
FAB	:	French American British classification
FLT3	:	Fms- like tyrosine kinase
FLT3-ITD	:	FLT3 – internal tandem duplucations
FLT3-L	:	FLT3- Ligand
FLU	:	Fludarabine
G-CSF	:	Granulocyte macrophage colony stimulating factor
GVHD	:	Graft Versus Host Disease
GVL	:	Graft Versus Leukemia
HB	:	Hemoglobin

LIST OF ABBREVIATIONS

Abb.		Full Term
HCTCI	**:**	Hemopoietic cell transplantation comorbidity index
HLA	**:**	human leucocytic antigen
HSCT	**:**	Hemopoietic stemm cell transplantation
MAC	**:**	myeloablative conditioning
MDS	**:**	Myelodysplastic syndrome
MDS/MPN	**:**	Myelodysplastic/Myeloproliferative neoplasm
MPO	**:**	Myeloperoxidase
MRD	**:**	minimal residual disease
MSD	**:**	matched sibling donor
MUD	**:**	matched unrelated donor
NK	**:**	natural killer cells
NPM	**:**	Nucleophosmin
NRM	**:**	non related mortality
PB	**:**	peripheral blood
PBSC	**:**	peripheral blood stem cell
PBSCT		peripheral blood stem cell transplantation
PCP	**:**	pneumocystis phneuminia
PI	**:**	prognostic index
PLT	**:**	Platelets
RIC	**:**	reduced intensity conditioning
SOS	**:**	Sinusoidal obstruction syndrome
t-AML	**:**	Therapy related Acute myeloid leukemia
TBI	**:**	Total body irradiation
TMA	**:**	thrombotic microangiopathy
TNC	**:**	total nucleated count
UCB	**:**	unrelated cord blood
URD	**:**	unrelated donor
VOD	**:**	veno occlusive disease
WBC	**:**	white blood count
WHO	**:**	world health organization

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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 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, 2013).**

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 **(Itır 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).**

Some trials showed significantly higher probability of relapse in BM recipients than in PBSC recipients, which might translate into better disease-free survival in PBSC

transplants compared with BM transplants **(Mielcarek. et al, 2012).**

Some trials showed PBSC recipients had significantly more grade 2-4 acute GVHD, chronic GVHD and extensive chronic GVHD compared with BM recipients, which resulted in significantly more patients who underwent PBPC transplant needed immunosuppressive treatment, and longer periods of corticosteroid use and hospitalization **(Friedrichs. et al, 2011).**

There was no difference in performance status, return to work, incidence of bronchiolitis obliterans, hematopoietic function, and secondary malignancies between the two groups in the long term in one trial. In contrast, another trial showed that late mortality due to chronic GVHD was more frequent in PBSC recipients compared with BM recipients.

The number of peripheral-blood stem cells is estimated with use of the cell-surface molecule CD34 as a surrogate marker. The number of CD34+ cells in blood can be increased by mobilizing them from the marrow with granulocyte colony-stimulating factor (G-CSF), which causes the proliferation of neutrophils and the release of proteases. Proteases degrade the proteins that anchor the stem cells to the marrow stroma and, together with protease-independent mechanisms, free the cells to enter the circulation **(Levesque. et al, 2004).**

While in autologous transplantation the studies published so far have shown that infusion of high doses of CD34 + cells leads to a faster hematopoietic engraftment and decreased transplantation related morbidity, within the allogeneic setting information regarding the optimal dose of hematopoietic progenitor cells remains controversial. While some studies have reported a positive impact on outcome in terms of faster engraftment and fewer infectious episodes by infusing high numbers of CD34+cells in patients undergoing bone marrow transplantation, other authors have shown an increased risk of acute or chronic graft-versus-host disease (GVHD) in patients receiving high doses of unmanipulated peripheral blood stem cells (PBSCs) **(Zaucha. et al, 2001).** Among recipients of CD34+-selected allogeneic transplants, the influence of the number of CD34 +cells on survival remains contradictory, since in CD34 +selected marrow transplantation higher cell doses lead to improved survival, while the opposite occurs with CD34+-selected PBSC transplants **(Urbano-Ispizua. et al, 2001).**

As cGvHD remains a significant problem after PBSC transplant, a major issue is to identify associated risk factors. Currently, there is no evidence that the factors commonly associated with GVHD after BM transplants have a role in the setting of PBSC transplant.

Furthermore, in contrast to results obtained after BM transplants, several studies, mainly in myeloablative PBSC transplantation from HLA identical sibling donors, demonstrated that the number of infused CD34 + cells strongly impacts the incidence of acute or chronic GVHD in PBSC transplant **(Pe´ rez-Simo´ n. et al, 2002).**

Aim of the work

The aim of the study is to assess CD34 in Egyptian patients with AML subjected to allogeneic peripheral blood stem cell transplantation and its relation to level of chronic graft versus host disease in the time period from January 2008 to December 2014.