



# **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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## LIST OF ABBREVIATIONS

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

## LIST OF ABBREVIATIONS

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