SERUM FERRITIN and SERUM HEPCIDIN LEVELS as PREDICTORS of EARLY POST HEMATOPOIETIC STEM CELL TRANSPLANTATION (<100D) INFECTIONS

Thesis

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List of Abbreviations

aGVHD	Acute Graft-versus-host disease
AIHA	Auto immune hemolytic anemia
ALL.....	Acute lymphoblastic leukemia
AML	Acute myelogenous leukemia
ATG	Antithymocyte globulin
BMP.....	Bone morphogenic protein
BMT.....	Bone marrow transplantation
BOOP	Bronchiolitis obliterans organizing pneumonia
BSI.....	Blood Stream Infection
CMI.....	Cell mediated immunity
CML	Chroic myelogenous leukemia
CMV	Cytomegalovirus
Dcytb.....	Duodenal cytoplasmic b-like protein
DFS	Disease free survival
DMT1	Divalent metal transporter 1
EBV.....	Epstein-Barr virus-related
ECF.....	Extra cellular fluid
ELISA.....	Enzyme-linked immunosorbent assay
EPO.....	Erythropoietin
FDA.....	Food and Drug Administration
Fe2+.....	Ferrous
Fe3+.....	Ferric
G-CSF.....	Granulocyte colony stimulating factor
GVHD.....	Graft-versus-host disease

List of Abbreviations (Cont...)

GVM	Graft-versus-malignancy
GVT	Graft-versus-tumor
HEPA	High-efficiency particulate air
HIF	Hypoxia-inducible factor
HLAs	Human leucocyte antigens
HPLC	High-performance liquid chromatography
HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem cell transplantation
HSV	Herpes simplex virus
IC	Iron chelation
IL-1	Interleukin-1
IL-2	Interleukin-2
IL-6	Interleukin-6
LONIPCs	Late-onset noninfectious pulmonary complications
LPI	Labile plasma iron
MDS	Myelodyplastic syndrome
MHC	Major histocompatibility complex
MMR	Measles mumps rubella
MRI	Magnetic resonance imaging
NTBI	Nontransferrin-bound iron
OS	Overall survival
PC	Pneumocystis carinii
PCR	Polymerase chain reaction
PTLD	Post-transplant lymphoproliferative disorder

List of Abbreviations (Cont...)

PUV	Psoralen plus ultraviolet
RIC	Reduced-intensity conditioning
SOS	Sinusoidal obstruction syndrome
TBI	Total body irradiation
TF	Transferrin
TFR1	Transferrin receptor 1
TGF-β	Transforming growth factor-β
TNF	Tumor necrosis factor
TMP-SMZ	Trimethoprim sulphamethoxazol
TRAP	Total radical antioxidant parameter of plasma
TRM	Transplant-related mortality
TSH	Thyroid-stimulating hormone
VOD	Veno-occlusive disease

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has become a curative treatment for hematologic malignancies. Although improvement of outcome has been achieved in recent decades by progress in various procedures such as the prevention of graft-versus-host disease (GVHD), infectious complications remain an important contributor to transplant-related mortality ***(Bjorklund et al., 2007).***

Iron overload is common in patients undergoing hematopoietic stem cell transplantation (HSCT) for hematologic disorders ***(Altes et al., 2004).***

A recently accumulated body of evidence suggests that iron overload is associated with adverse clinical outcomes in HSCT ***(Altes et al., 2009).***

Other studies have shown that pretransplant iron overload in autologous or allogeneic HSCT was a risk factor associated with post transplant complications, such as mucositis, bacterial, and fungal infection, and hepatic veno-occlusive disease (VOD) ***(Kataoka et al., 2009).***

High pretransplant serum ferritin level was strongly associated with lower overall and disease free survival (OS, DFS) in patients with allogeneic HSCT that was performed as a treatment for acute leukemia and myelodyplastic syndrome (MDS) ***(Armand et al., 2007).***

Pretransplant serum ferritin level was a risk factor for the occurrence of BSI (Blood Stream Infection) within 100 days after allo-HSCT ***(Tachibana et al., 2010).***

Hepcidin, first identified in human blood and urine as an antimicrobial small peptide, is now considered to be a central molecule that regulates iron metabolism ***(Park et al., 2001).***

Hepcidin decreases iron absorption from the intestine and blocks its release from iron stores by down regulating the expression of the cellular iron exporter, ferroportin. Therefore, it is hypothesized that serum hepcidin level could be a useful predictor of iron overload and inflammatory condition prior to HSCT ***(Ganz et al., 2005).***

Consistent association of high hepcidin levels with high risk for developing bacterial infection were observed when analyses were confined to either the low-or high-ferritin subgroups. These finding collectively suggest that hepcidin can be used as better predictor of documented bacterial infection than serum ferritin level ***(Murphy et al., 2007).***

AIM OF THE WORK

Was to compare between pretransplant serum ferritin and serum hepcidin levels as predictors of early (before 100 days) post HSCT infections.

Chapter (1)

OVERVIEW OF HEMATOPOIETIC STEM CELL TRANSPLANTATION

What Is a Hematopoietic Stem Cell?

A hematopoietic stem cell is a cell isolated from the blood or bone marrow that can renew itself, can differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis-a process by which cells that are detrimental or unneeded self-destruct ***(Sharp et al., 2000).***

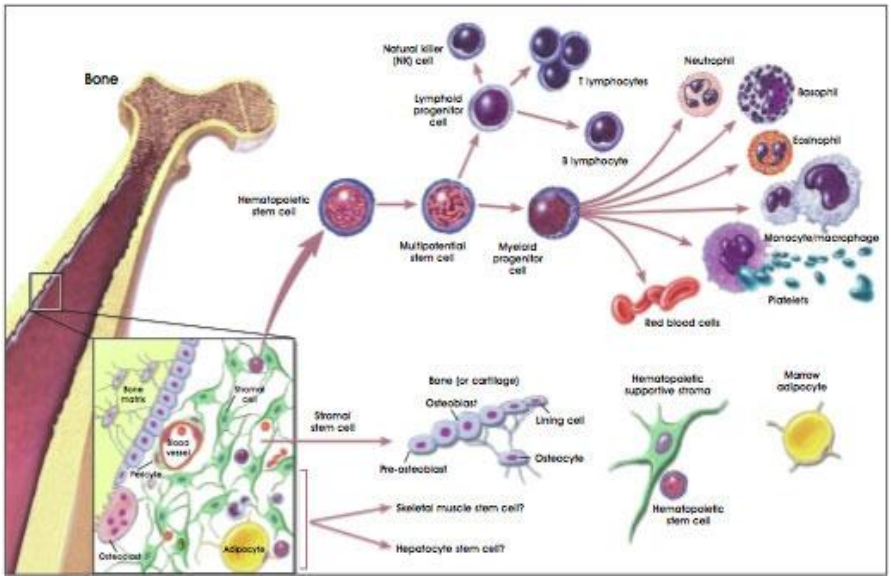

Fig. (1): Hematopoietic and Stromal Stem Cell Differentiation ***(Terai et al., 2005).***

Hematopoietic stem cell transplantation (HSCT) is the transplantation of multipotent hematopoietic stem cells, usually

derived from bone marrow, peripheral blood, or umbilical cord blood. Hematopoietic stem cell transplantation remains a risky procedure with many possible complications; it has traditionally been reserved for patients with life-threatening diseases. While occasionally used experimentally in nonmalignant and nonhematologic indications such as severe disabling auto-immune disease and cardiovascular disease, the risk of fatal complications appears too high to gain wider acceptance ***(Tyndall et al., 2000).***

Georges Mathé, a French oncologist, performed the first bone marrow transplant in 1959 on five Yugoslavian nuclear workers whose own marrow had been damaged by irradiation caused by a Criticality accident at the Vinča Nuclear Institute, but all of these transplants were rejected. Mathé later pioneered the use of bone marrow transplants in the treatment of leukemia ***(Burt et al., 2008).***

Types of stem cell transplantation:

Types of hematopoietic stem cell transplantation (HSCT) are typically categorized based on the source of progenitor cells used in the transplant. These cells have 3 main sources: the patient (an autologous transplant), someone besides the patient (an allogeneic transplant), or donated umbilical cord blood (a cord blood or umbilical cord blood transplant). Each of these sources of cells has specific advantages and disadvantages, and each has found particular applications in the care of patients with oncologic or immunologic disorders ***(Jonathan, 2011).***

Autologous

Autologous transplantation is typically used as a method of returning the patient's own stem cells as a rescue therapy after high-dose myeloablative therapy. This is generally used in chemo sensitive hematopoietic and solid tumors to eliminate malignant cells by administering higher-dose chemotherapy than could normally be tolerated by the bone marrow of the patient, with the target of increasing the chances of killing remaining tumor cells. The high dose chemotherapy is then followed with subsequent rescue of the host's bone marrow with previously collected autologous stem cells. Immunosuppression is not required after autologous transplantation because the immune system that is reconstituted is that of the original host. Because the native immune system returns after autologous transplant, this technique is not used for correction of immunodeficiencies ***(Jonathan 2011)***.

Allogeneic

Allogeneic transplantation refers to the use of stem cells from a donor source other than the subject. The source of donated stem cells (the donor) may be genetically related or unrelated to the recipient. This type of transplant is used in the context of many malignant and nonmalignant disorders to replace a defective host marrow or immune system with a normal donor marrow and immune system. The degree of HLA match between the donor and the recipient is perhaps the most important factor in these transplants; well-matched transplants

decrease risks of graft rejection and graft versus host disease (GVHD), both of which are among the most serious sequelae of transplantation ***(Jonathan 2011)***.

Cord blood transplantation refers to the use of hematopoietic stem cells collected from the umbilical cord and placenta. The use of cord blood transplantation has rapidly increased because of several favorable factors, including ease of collection, expanded and prompt availability, no risk to the donors, a decreased risk of adverse effects (eg, GVHD, transmission of infections), and increased tolerance to HLA-mismatch ***(Koh et al.,2004).***

Use of cord blood as a source of donor stem cells can be limited by the quantity of cells available in a typical sample. Improved collection techniques have increased the size of aliquots available from a given donor and are making this source available to more patients. Additional research is exploring the use of multiple cord blood transplants, in which multiple cord blood donors are used during the same transplantation procedure to improve engraftment times ***(Lister et al.,2007).***

In November 2011, the US Food and Drug Administration (FDA) approved the first umbilical cord blood product for use in stem cell transplantation. The product contains hematopoietic progenitor cells from human cord blood (HemaCord, New York Blood Center) ***(FDA, 2011)***.