Introduction

Hematopoietic stem cell transplantation (HSCT) is well established as therapy for hematologic malignancies as well as many non-malignant disorders ***(Crouch et al., 2006)***.

Conventional allogenic hematologic cell transplantation is potentially curative treatment option for various hematologic diseases due to in part high dose conditioning and in part to graft versus host effects. Reduced intensity or non-myeloablative conditioning regimens have relied mostly on graft- versus- host tumour effects for disease control. However both HSCT modalities have been associated with organ toxicities and graft versus host disease, resulting in substantial non-relapse mortality ***(Sorror, 2010)***. Moreover, patients with coexisting medical problems may suffer increased toxicity and reduced quality of life after autologous HSCT ***(Lalonte et al., 2008)***.

Accordingly, patient's comorbidities are being increasingly analyzed as predictors for outcome after HSCT ***(Barlia et al., 2010)***.

Various comorbidity indices have been developed in attempts to facilitate pre-transplantation patient counseling in addition to patient's characteristics and disease state.

Most of these indices including cardiac, GIT, cardiovascular, hepatic, psychiatric, rheumatologic, renal, pulmonary comorbidities as well as diabetes mellitus, obesity and infections ***(Pollack et al., 2009).***

Aim of The Work

The aim of this work is to investigate retrospectively and prospectively the impact of various pretransplant comorbidities on outcome of patients with hematological diseases treated with HSCT either-allogenic or autologous-in relation to treatment related mortality and disease related mortaliy with specific emphasis on overall survival.

Chapter (1)
Hematopoietic stem cell transplantation

Introduction:

History of hematopoietic cell transplantation:

There is no doubt that hematopoietic stem cell transplantation (HSCT) has represented one of the most innovative treatments of the last decades, as well as one of the most significant medical feats of human bio-solidarity ***(Porta et al., 2008)***.

Hematopoietic stem cell transplantation (HSCT) is the process and intravenous infusion of hematopoietic stem and progenitor cells to restore normal hematopoiesis and/or treat malignancy. The term " hematopoietic stem cell transplantation" has replaced the term "bone marrow transplantation" (BMT) because hematopoietic stem cells can be derived from a variety of sources other than the bone marrow, including the peripheral blood and umbilical cord blood ***(Weissman, 2000).***

The history of hematopoietic stem cell transplants originated with scientists attempting to treat individuals who had been exposed to radiation ***(Hildreth et al., 2009).***

In 1959 Edward Donnall Thomas, an American physician, conducted the first human hematopoietic stem cell transplant, which was between twin sisters. One sister with end-stage leukemia received total body irradiation to destroy the cancer and then received a bone marrow transplant from her healthy sister. The result was the regression of the recipient sister's end-stage leukemia for three months ***(Thomas and Donnall, 1995).***

The following years brought in human leukocyte antigen (HLA) typing, which allowed physicians to find histocompatible donors for recipients. This breakthrough led to the first hematopoietic stem cell transplant between non-identical siblings, conducted by Robert Alan Good in 1969. The pioneering work by Thomas and Good led to the establishment and use of hematopoietic stem cell transplantation to treat various blood-borne diseases, including cancers, genetic diseases, and immunodeficiency syndromes ***(Samavedi et al., 2010).***

Despite the promises offered by this possibly life-saving treatment, there are risks associated with this procedure. For instance, infection is an associated risk because of the need to use immunosuppressants. With a weakened immunological system, pathogens can easily colonize the body ***(Copelan, 2006).***

The most important risk associated with HSCT, however, is rejection. There are two forms of rejection. First, the rejection of the graft by the host is caused by the response of the immune system to the infusion of foreign cells. The immune cells attack and destroy the graft cells, rendering the graft ineffective. The second, and most dangerous, form is rejection of the host by the graft. In this case, the graft mounts an immune attack on the host, leading to destruction of the host's tissues. This form of rejection leads to a set of graft vs. host diseases. As the technology behind HSCT advances, new drugs have been discovered that help reduce the risk of a patient contracting a GVHD ***(Hildreth et al., 2009).***

HSCTs have become a common practice with about 10, 000 procedures occurring worldwide every year since the early 2000s. Transplantation has provided many patients with life-saving treatment as well as a better quality of life ***(Samavedi et al., 2010).***

Types of stem cell transplants:

According to donors, HSCT can be divided into autologous, allogeneic and umbilical cord blood (UCB) transplantation. Syngeneic HSCT refers to HSCT from an identical twin, and is uncommonly performed ***(Campbell, 2012).***

For allogeneic and UCB transplantations, the choice of donors is determined by the human leucocyte antigen (HLA) compatibility at the A, B, C (class I), and DRB1 and DQB1 (class II) genetic loci. Sibling donors with identical alleles at these loci are most suitable, followed by related or unrelated donors with the best matching ***(Leung and Kwong, 2009).***

There are 3 basic types of transplants. They are named based on who gives the stem cells:

Autologous Stem Cell Transplantation :

This type of transplantation involves the use of a patient's own stem cells. The stem cells are collected from marrow, blood, and then frozen. The thawed cells are returned to the patient after he or she has received intensive chemotherapy and/or radiation therapy for his or her disease as shown in figure (1) ***(Campbell, 2012).***

Autologous transplant is aiming to give the patient high doses of chemotherapy with or without radiation that would otherwise be too toxic to tolerate because the marrow would be severely damaged. Such high doses of treatment can sometimes overcome resistance of the disease to standard doses of chemotherapy ***(Arfons et al., 2009).***

Autologous transplantation requires that an individual have sufficient number of healthy stem cells in the marrow or blood. For example, in patients with acute leukemia,

remission must be achieved before the patient's marrow or blood is harvested and frozen for later use ***(Campbell, 2012).***

Since the stem cells are the recipient's own, graft-versus-host disease (GVHD) is rarely a problem. However, the patient's immune system does require time to recover after the procedure, and risk of relapse of the person's disease may be higher ***(Armitage, 2007).***

To prevent this, anti-cancer drugs to be given or treat patient stem cells in other ways to reduce the number of cancer cells that may be present. Some centers treat the stem cells to try to remove any cancer cells before they are given back to the patient. This is sometimes called "*purging*." It isn't clear that this really helps, as it has not yet been proven to reduce the risk of cancer coming back (recurrence) ***(Campbell, 2012).***

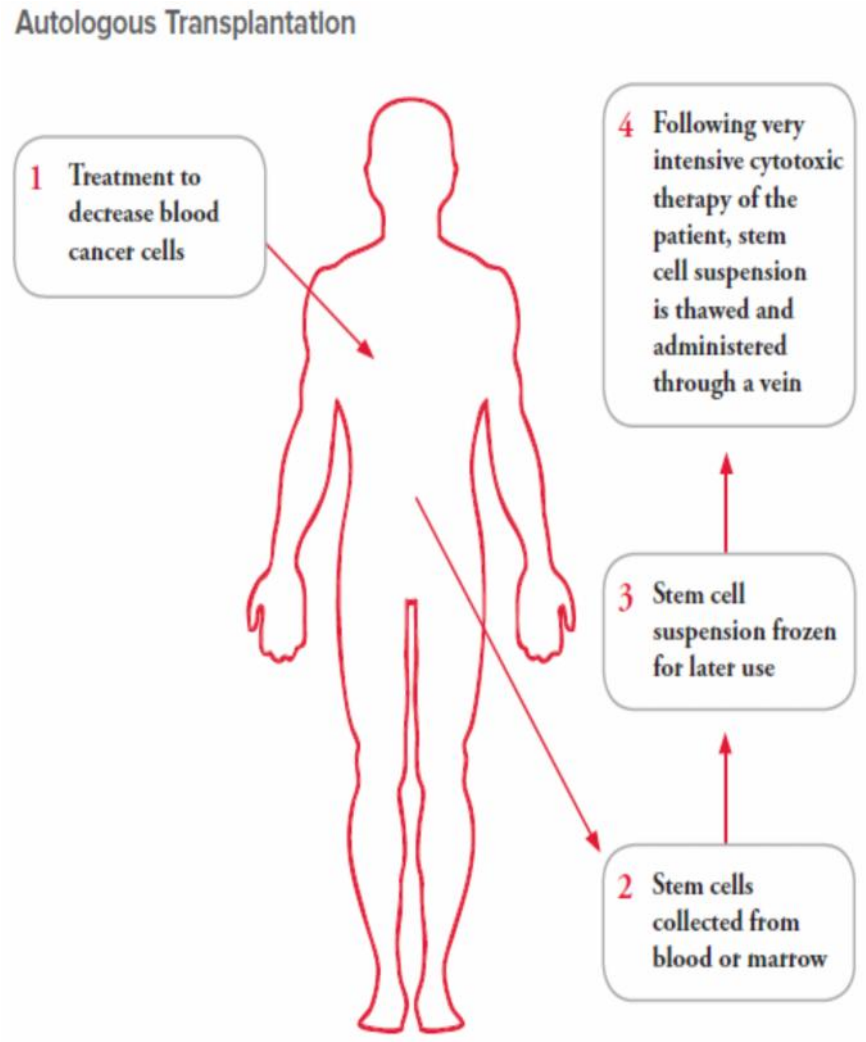

Figure (1): The steps involved in autologous stem cell transplantation ***(Lowsky et al., 2012).***

Autologous Transplantation without Cryopreservation:

Studies have shown that peripheral blood stem cells (PBSCs) can be stored safely at 4°C for at least 5 days, while the patient receives high-dose chemotherapy. Viability of stem cells decreases progressively from day 5 onwards ***(Anazi, 2012).***

The use of noncryopreserved stem cells in transplantation has the following advantages: (1) simplicity of implementation and allowing auto-HSCT to be done entirely as outpatient, (2) reduction of transplant costs, (3) expansion of the number of medical institutions that offer stem cell therapy, (4) prevention of DMSO toxicity, (5) saving time between the last induction therapy and high-dose therapy, and (6) no significant reduction in viability of collected stem cells provided infusion is done within 5 days of collection. On the other hand, noncryopreserved HSCT has the following disadvantages: (1) limitation of the use of standard high-dose schedules employed in auto-HSCT, (2) plenty of coordination between various teams is required regarding timing of stem cell mobilization, apheresis, administration of high-dose therapy, and stem cell transfusion, and (3) inability to store part of the collection and reserving it for second transplant or other purposes in case a rich product is obtained ***(Ramzi et al., 2012).***

Studies comparing overnight storage of autologous stem cell apheresis products at 4°C with immediately cryopreserved products showed no statistically significant difference between the two groups regarding viability of collected stem cells, neutrophil and platelet engraftment days, safety, and even long-term outcome of the primary disease. Additional benefits of overnight storage of harvested products were reduction in costs and processing time ***(Donmez et al, 2007).***

Tandem transplants:

Doing 2 autologous transplants in a row is known as a *tandem transplant* or a *double autologous transplant.* In this type of transplant, the patient gets 2 courses of high-dose chemo, each followed by a transplant of their own stem cells. All of the stem cells needed are collected before the first

high-dose chemo treatment, and half of them are used for each transplant. Most often both courses of chemo are given within 6 months, with the second one given after the patient recovers from the first one ***(Bahthia, 2011).***

Tandem transplants are most often used to treat multiple myeloma and advanced testicular cancer, but doctors do not always agree that these are really better than a single transplant for certain cancers. Because this involves 2 transplants, the risk of serious outcomes is higher than for a single transplant.

Tandem transplants are still being studied to find out when they might be best used. Sometimes an autologous transplant followed by an allogeneic transplant might also be called a tandem transplant ***(Brunstein and Weisdorf, 2009).***

Standard Allogeneic Stem Cell Transplantation :

This type of transplantation involves the use of donor stem cells, which can come from a related or unrelated donor as shown in figure (2). Siblings have the potential to match the patient's tissue type most closely, because the patient and the sibling donor have received their genes from the same parents. However, siblings do not always have closely matched tissue types ***(Campbell, 2012).***

The term “unrelated donor" (URD) is sometimes used to describe a donor who is not a blood relative. An unrelated donor is found by searching registries of volunteer donors for an individual who happens to be identical or very similar in tissue type to the patient.

Stem cells from cord blood may also be a source for allogenic transplants for certain patients.

When a transplant is successful; the donor stem cells can restore normal marrow and may provide the only long-term cure of the patient´s disease ***(Lowsky et al., 2012).***

The immune system and the blood system are closely linked and cannot be separated from each other. Because of this, allogeneic transplantation means that not only the blood system but also the immune system of the donor is transferred to the recipient. As a result, these effects are possible:

- Immune rejection of the donated stem cells by the recipient (host-versus-graft effect)
- Immune reaction by the donor cells against the tissues of the recipient (graft-versus-host disease [GVHD]).

Before a standard allogeneic transplant, patients receive conditioning regimen in the form of high doses of chemotherapy and sometimes radiation therapy, destroys the cancer cells and suppresses the patient's immune system; therefore, the immune system is less able to attack the transplanted donor stem cells ***(Arfons et al., 2009).***

One of the benefits of an allogeneic transplant is that the donor immune system can recognize remaining cancer cells that have survived even high doses of chemotherapy, with or without radiation, and kill them, helping to prevent disease relapse ***(Spellman et al., 2012).***

Graft-versus-disease (GVD) effect that may be even more important than the very intensive therapy administered to destroy cancer cells.

The immune reaction, or GVHD, is treated by giving drugs to the recipient after the transplant to reduce the ability of the donated immune cells to attack and injure the patient's tissues. Over time, the new immune system grown by the donor cells may develop tolerance to the host (the patient),

and the immunosuppressing medications can be weaned and eventually stopped in some cases ***(Jagasia et al., 2011).***

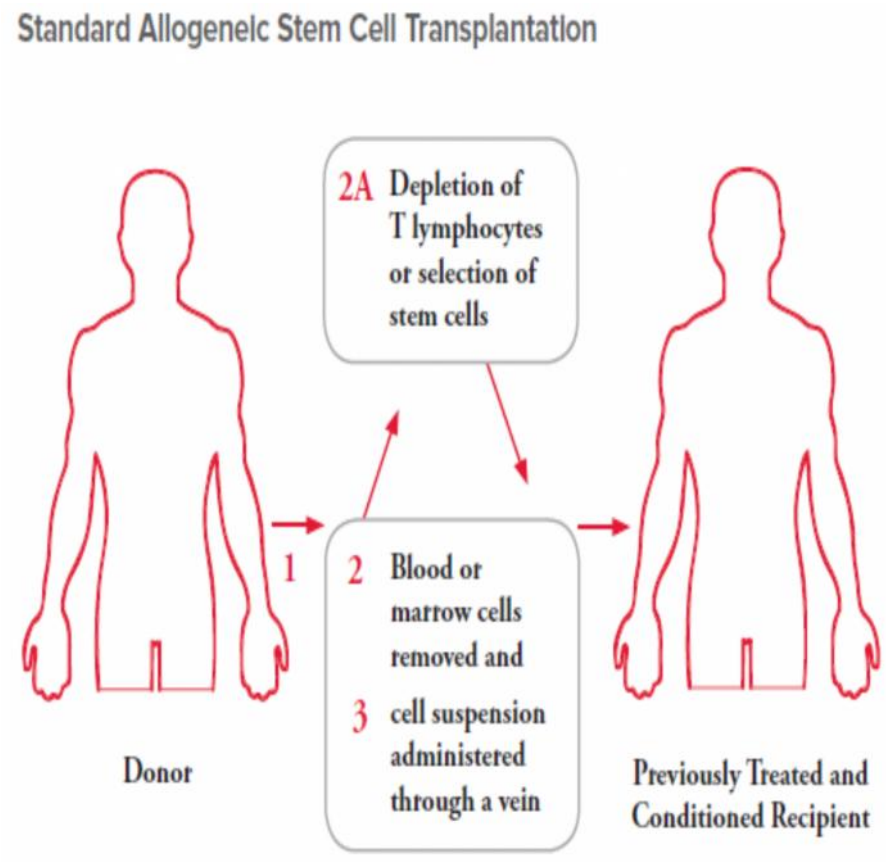

Figure (2): Steps of standard allogenic stem cell transplantation ***(Lowsky et al., 2012).***

Reduced-Intensity Allogeneic Stem Cell Transplantation:

This type of transplantation involves using less-intense conditioning treatment to prepare for the transplant as compared to standard allogeneic transplantation.

With a standard allogeneic transplant, the conditioning regimen destroys most of the cancer cells. However, a reduced-intensity allogeneic transplant relies on the donor immune cells to fight the disease ***(Spellman et al., 2012).***

Reduced-intensity allogeneic transplants (sometimes called "nonmyeloablative transplants") may be an option for certain patients who are older, who have organ complications or who are otherwise not healthy or strong enough to undergo standard allogeneic transplantation. However, reduced-intensity allogeneic transplants carry many of the same risks as standard allogeneic transplants, but like standard-intensity allogeneic transplants, also provide benefit via the GVD effect to help prevent disease relapse ***(Lowsky et al., 2012).***

Research study results to date indicate that reduced-intensity allogeneic transplants are more effective as a treatment for some types and/or stages of blood cancer. Research indicates that reduced-intensity allogeneic transplants may be effective in treating certain patients with chronic myeloid leukemia (CML), acute myeloid leukemia (AML), non-Hodgkin lymphoma (NHL), and chronic lymphocytic leukemia (CLL), or myelodysplastic syndromes (MDS) ***(Jagasia et al., 2011).***

The conditioning regimen for a reduced-intensity allogeneic transplant does not destroy many cancer cells. However, it suppresses or weakens the patient's immune system so that it cannot attack the donor cells. The cells for a reduced-intensity transplant can come from a family member, an unrelated donor or, less often, a cord blood unit. The donor cells grow a new immune system and the new immune cells destroy the cancer cells ***(Spellman et al., 2012).***

Syngeneic Stem Cell Transplantation:

This type of allogenic transplant in the case of the donor and recipient are twins with identical genetic makeup and the same tissue type.

With this kind of transplantation, donor cells are not rejected and the recipient's tissues are not attacked by the donor's immune cells. No treatments are needed to prevent graft rejection or GVHD. However, no beneficial GVD effect is expected either ***(Spellman et al., 2012).***

Furthermore, as with autologous transplants, relapse of the patient's disease is more common than with other types of donors. Long-term remission is achieved in some of these patients due to the conditioning regimen effects and the infusion of normal stem cells ***(Lowsky et al., 2012).***

Indications of stem cell transplantation:

Stem cell transplants are used to replace bone marrow that isn't working or has been destroyed by disease, chemo, or radiation. In some diseases, like leukemia, aplastic anemia, certain inherited blood diseases, and some diseases of the immune system, the stem cells in the bone marrow don't work the way they should ***(Arfons et al., 2009).***

In order to restore blood cell production, a patient may be given healthy stem cells. These may be the patient's own stem cells which were collected either prior to the disease or before intensive treatment started. This is known as an autologous transplant or an autograft ***(Campbell, 2012).***

If healthy stem cells cannot be obtained from the patient they may be from a donor (e.g. from a brother or sister or an unrelated person). This is particularly beneficial in eliminating malignant disease from the marrow. A relatively new source of stem cells is the blood from the umbilical cord and placenta of a newborn infant ***(Arfons et al., 2009).***

A stem cell transplant from another person can also help treat certain types of cancer in a way other than just

replacing stem cells. Donated cells can often find and kill cancer cells better than the immune cells of the person who had the cancer ever could. This is called the "graft-versus cancer" or "graft-versus-leukemia" effect. It means that certain kinds of transplants actually help fight the cancer cells, rather than simply replacing the blood cells ***(Campbell, 2012).***

Malignant/premalignant diseases:

- Acute lymphoblastic leukemia (ALL)
- Acute myeloid leukemia (AML)
- Chronic myeloid leukemia (CML)
- Juvenile myelomonocytic leukemia
- Myelodysplastic syndromes
- Plasma cell disorders
- Hodgkin and non-Hodgkin lymphoma

Nonmalignant diseases:

- Inherited red cell disorders - Pure red cell aplasia, sickle cell disease, beta-thalassemia, and others
- Marrow failure states - Severe aplastic anemia, Fanconi anemia, and others

Rare indications:

- Acquired immune deficiency syndrome - HIV (One HIV-infected patient with acute myeloid leukemia [AML] was treated with allogeneic bone marrow transplantation from a donor who was lacking the CCR5 cell surface protein that is crucial for HIV entry into human cells. At last report, the patient was doing well, having remained off antiretroviral therapy for 2 years following BMT.

- Inherited metabolic disorders - Adrenoleukodystrophy, Hurler syndrome, metachromatic leukodystrophy, osteopetrosis, and others
- Inherited immune disorders -Severe combined immunodeficiency, Wiskott-Aldrich syndrome, and others
- Autoimmune diseases (experimental) - Systemic sclerosis, severe systemic juvenile rheumatoid arthritis, lupus, multiple sclerosis, Crohn disease, and others.

Allogeneic SCT is performed commonly in patients with AML, ALL, resistant CML, aplastic anemia, MDS and β thalassemia. However, autologous SCT is commonly performed in patients with Hodgkin, non Hodgkin lymphoma and multiple myeloma.

Tissue typing:

The MHC locus is highly polymorphic, representing over 800 alleles described to date, and new molecules continue to be described.

The reason for this diversity is believed to be the evolutionary pressure on genetic change required for adapting molecules to emerging variations in micro-organism encountered during the human diaspora in to new environmental niches over the last 100, 000 years ***(Jagasia et al., 2011).***

HLA typing involves molecular or serologic typing of blood leucocytes to determine HLAA, B, C (MHC class I) and DR, DP, DQ types (MHC class II) as shown in figure(3).

Clinical transplant results clearly show the advantage, in both related and unrelated donor searches, of finding the closest HLA identity possible ***(Spellman et al., 2012).***