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Review Article

Haematopoietic Stem Cell Transplantation

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ABSTRACT

Around 50,000 hematopatio stem cell transplants are done each year for the treatment of lymphoma, leukemia, immune deficiency diseases, and immunodefetocs, and hematopathies, and myelogenous and myelomen syndromes. Prior to transplantation, patients undergo myeloablative chemoradiation, after which they receive extensive "rescue" cell treatment a method of allogeneic HSCT is done by reinfusing the patient's own blood-derived stem cells, which are collected before transfusion. The stem cells used in allogeneic HSCT are human leukocyte antigens (HLA) balanced Allogeneic survival after transplantation depends on donor/patient pairing, the graft/recipient response, and the frequency of a donor leukemia impact. This article reviews the biology of stem cells, clinical efficacy of HSCT, transplantation procedures, and potential complications.

Keywords: *Haematopoietic Stem, Cell Transplantation*

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is the transplantation of multipotent hematopoietic stem cell or blood, usually derived from bone marrow, peripheral blood stem cells, or umbilical cord blood. Stem cell transplantation is a medical procedure in the fields of hematology and oncology, most often performed for people with diseases of the blood, bone marrow, or certain cancers.

Stem cells have the remarkable potential to develop into many different cell types in the body during early life and growth. In addition, in many tissues they serve as a sort of internal repair system, dividing essentially without limit to replenish other cells as long as the person or animal is still alive.

When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell. Stem cells, under certain physiologic or experimental conditions, can be induced to become tissue- or organ-specific cells with special functions. In some organs,

such as the gut and bone marrow, stem cells regularly divide to repair and replace worn out or damaged tissues.

Hematopoietic stem cells (HSCs), are multipotent stem cells that give rise to all the blood cell types from the myeloid (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells), and lymphoid lineages (T-cells, B-cells,NK-cells). The definition of haematopoietic stem cells has undergone considerable revision in the last two decades. Hematopoietic tissue contains cells with long-term and short- term regeneration capacities and committed multipotent, oligopotent, and unipotent progenitors. HSCs constitute 1:10.000 of cells in myeloid tissue.

Although Hematopoietic stem-cell transplantation was originally conceived more than 50 years ago as a treatment for injury from irradiation and, later, for cancer, associated problems needed to be solved before the procedure could be used clinically. Bone marrow, the source of hematopoietic stem cells, is not a solid organ but is rather diffuse and not directly accessible. Furthermore, hematopoitic cells can initiate immune reactions that may thwart transplantation.

SHORT HISTORY

More than half a century of studies found that total-body irradiation seriously affects the gastrointestinal and central nervous systems. For smaller doses, there is a direct correlation between blood loss and infection. In animal models, transplantation of genetically similar (syngeneic) marrow averted death Grafts taken from histocompathogenic litter obtained overall survival. [1] [2]Grafts taken from histocompathogenic litter obtained overall survival. Post transplantation of incompatible marrow, which is not similar to the recipient's lymphocytes and leads to an inflammatory condition in the target tissues, known as graft-versus-host disease (GVHD). [3]Hematopo-differentiation triggered by methotrexate suppression. Instead of whole-body irradiation, we gave our patients a preparative regimen which allowed total engraftment. [4]

With the findings of previous animal experiments, Thomas was the first to apply early research on leukemia care in humans.In 1959, he and his colleagues announced that a case where a leukemic patient received an end-of-of-life regimen of total-body irradiation and was accompanied by administration of their identical twin's marrow infusions. [5]

HLA was discovered in the early 1960s, allo-transplantation became feasible. The HLA genes are located on chromosome 6 and inherited as haplotypes.

The odds of two siblings being HLA alike are therefore around one in four or four, or five siblings out of a six. Bone marrow transplantation was successful because the recipient did not refuse the graft. [6] Other Thomas and his colleagues successfully treated several end-stage leukemia patients by ablating the whole body, along with HLA-matched donor marrow, with total-body irradiation and cyclophosphamide. [7] Around half of the patients' leukemic transplants were successful in the first week after the procedure. [8]

CURRENT KNOWLEDGE AND THEORY

Mature blood cells are generated by pre-precurs which have in turn originated from hematopiac progenitors.Heopi- and haematopoic stem cells may develop self-renewing stem cells, which have the ability to reproduce indefinitely. Really, a single stem cell can effectively re-treatsolve the whole irradiated animal system. [9]

A gene (figure 1) is a molecular unit of heredity of a living organism. It is a name given to some stretches of DNA and RNA that code for a type of protein or for an RNA chain that has a function in the organism. Living beings depend on genes, as they specify all proteins and functional RNA chains. Genes hold the Information

to build and maintain an organism's cells and pass genetic traits to Offspring.

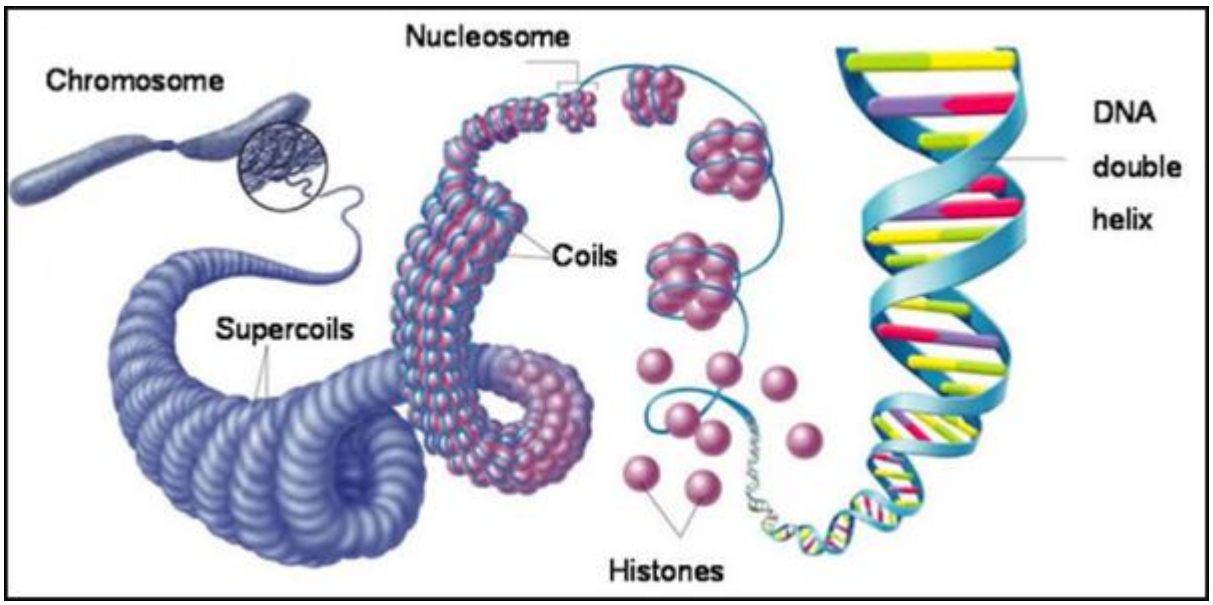

Figure-1: gene - a molecular unit of heredity of a living organism

The vast majority of living organisms encode their genes in long strands of DNA (figure 2). DNA (deoxyribonucleic acid) consists of a chain made from four types of nucleotide subunits, each composed of: a five-carbon sugar (2'-deoxyribose), a phosphate group, and one of the four bases adenine(A), cytosine(C), guanine (G), and thymine(T). The most common form of DNA in a cell is in a double helix structure, in which two individual DNA strands twist around each other in a right-handed spiral.

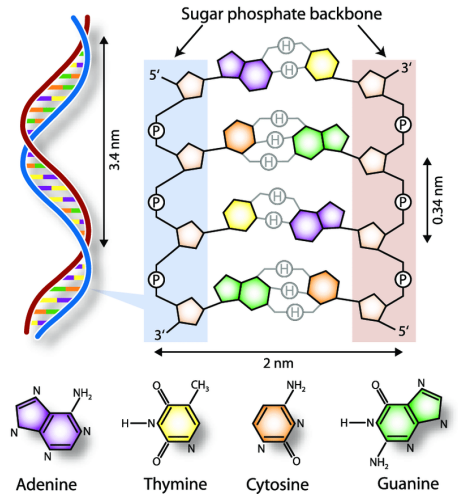

Figure-2: Schematic picture of DNA — twisted double helix

Within a gene, the sequence of bases along a DNA strand defines a messenger RNA sequence, which then defines one or more protein sequences. The relationship between the nucleotide sequences of genes and the amino- acid sequences of proteins is determined by the rules of translation, known collectively as the genetic code.

Cancer treatment is successful against quickly proliferating cells. Malignant and quiescent stem cells cannot be altered. Malignant and natural stem cells repair DNA successfully, prevent apoptosis, and detoxify harmful substances. [10]Thus, while chemo will totally kill the stem cells, cancer returns. Studies of advanced bone marrow analysis and also in cases of BCR-ABL (molecularly targeted) target leukemia have indicated leukemic progenitor cells, which promote relapse. There are malignant stem cells that can tolerate 100% of the total-body irradiation and chemotherapy prior to an HD treatment. These cells can be eliminated by using immunomodulators.

Allogeneic grafts elicit immune responses to histicity. The intensity of the reaction increases as the degree of peptide receptor class I and class II cell-presentation increases. Allografts ought to be rejected in favor of histocompatibility. The strength of the reaction depends on the degree of contact, which is based on a complex biology in which different polymorphic class I and class II cell-peptides bind small peptides from proteins that have been digested.

The most adverse histocompatibility antigens (HLA) of donor and receiver should be avoided. Where there are several peptides derived from degraded HLA molecules, and when HLA molecules are present on cell surface antigen-presenting sites, the speed of the reaction will increase.

On the other hand, "minor histotopes" are monpolypeptides produced from distinct polymorphic proteins (which may vary between donors)." HLA molecules are able to present the minor antigens, and this is how the weaker responses are initiated. little antigens on the male chromosomes contribute to the higher occurrence of GVHD and the lower relapse risk of underlying conditions.

STEM CELL FUNCTION AND DIFFERENTIATION

Stem cells are present in the body and are pluripotent, capable of infinite self-renewal and development of highly advanced progeny. The various proliferative properties and roles of stem cells vary based on their location or compartments. Hematopo-stem cells are distinguished by their ability to replicate and differentiate into all blood lineages. [11]Hematopoepis is a developmental mechanism in which HSCs settle on a particular blood lineages, creating the different bloods. [12]

Maturation of suitable numbers and forms requires a diverse regulatory system that is incompletely understood M cellular interactions with soluble and extracellular cytokines regulate hematopoic cell differentiation and proliferation.Thus, the earliest human HSCs express the cell surface antigen CD34 and receptors for the early hemopoietic growth factors kinase [flk-1], endothelial growth factor, and vascular endothelial growth factor (VEGF) kinases: KDR and Flt 3." [13]BM or peripheral blood HSCs may be harvested for transplantation The time required for engraftment of hematoprotic cells after BM ablation depends on their movement and return to the recipient's BM niches. HSC “homing” is a multistep process involving sequential activation of adhesion molecules.7 The chemokine stromal cell-derived factor-1 (SDF-1) was the first identified chemoattractant for monocytes, lymphocytes, and CD34+ cell homing. [14][15]

RATIONALE FOR HEMATOPOIETIC STEM CELL TRANSPLANTATION – HOW TRANSPLANTATION WORKS

HSCT indications depend on the patient's medical condition, the therapeutic aims, and stem cells.in 2006, the Center for International Blood and Marrow Transplant Research (CIBM) found that the number of potential indications for stem-cell transplants included hematological conditions (in other words, malignant or pre-malignant conditions) to be universal.This represents 33% of allogene stem cell transplants, 16% of acute lymphoblastic, 6% of chronic leukem, and 18% of multiple myeloma.

Table-1: Disorders treated by hematopoietic stem cell transplantation (HSCT)

The use of allogeneic HSCT for hematological malignancies in the 1980s and early 1990s was largely restricted to younger patients (≤45 years old) with a human leukocyte antigen (HLA)-identical sibling donor.supportive treatment of less-intensive protocols and GvHD prophylaxis have seen a rise in the use of allogeneic HSCT in older patients Around the age of

50 years, there were 4% of allogeneic HSCT receivers in 1987 and 1992 Of allogeneic HSCT recipients, 33% were 50 or older, and 11% were over 60.This has been made simpler by unrelated donor registries, such as the Anthony Nolan Trust in the UK. less than 10% of HSCTs for hematological neoplasms unrelated donors in 1987; more than 40% in 2006.HSCT requires higher doses that would otherwise be lethal in a traditional treatment setting allogeneic or autologous HSCs are used to treat life-threatening myelosuppression. Most successful in the treatment of myelodiscancer is administering autologous stem cell transplantation in correlation with response to dose-limiting toxicities of the treatment. In allogene HSCT, the conditioning regimen removes malignant cells, ineffective hematopoeitic cells, and non-leukocytic immunosuppressive cells, or those that have been recognized as international.Although HSCT was originally regarded as a way of rescuing patients from therapy-induced marrow aplasia, it is now accepted thatalloreactive donor cells confer a substantial graft-versus-tumor (GvT) effect, which contributes to cancer eradication.

SOURCE OF STEM CELL

Bone marrow collected while the donor was under light or moderate anesthesia is an option in the case of posterior iliac hematology, the first having been extracted by means of repeated aspiration of the posterior/a needle aspiration of the posterior crests.Often, however the risks of harvesting normally vanish in two weeks, and the severity of the side effects is low (two deaths in 8000 collections). [16]

Peripheral blood is the most suitable source of hematopo-and- stem cells for of these apply. Selection of HSC source autologous and allogeneic transplantations. As compared to commonly used methods, peripheral blood stem cells have a far higher reconstitute Formalization rate with allo-transplantation, but peripheral blood stem cells, which produce more T cells than marrow does, there is a rise in the risk of HIV-AIDS and cancer development In an autologous situation, the patient transplants his own cells into the body; a syngeneic, includes related cells from the patient's own body; and allogentic conditions apply where all depends on donor availability and on

Nonmalignant

- Aplastic anemia
  - Fanconi anemia
  - Diamond–blackfan syndrome
- Sickle cell disease
- Thalassemia
- Paroxysmal nocturnal hemoglobinuria
- Chediak–Higashi syndrome
- Chronic granulomatous disease
- Glanzmann thrombasthenia
- Osteopetrosis
- Lysosomal storage disorders
  - Gaucher disease
  - Niemann–Pick
- Mucopolysaccharidosis
- Glycoproteinoses
- Immune deficiencies
- Ataxia telangiectasia
- DiGeorge syndrome
- Severe combined immunodeficiency (SCID)
- Wiscott–Aldrich
- Kostmann syndrome
- Shwachman–Diamond syndrome

Malignant

- Leukemias
  - Acute myelogenous leukemia
  - Acute lymphoblastic leukemia
  - Hairy cell leukemia
  - Chronic lymphocytic leukemia
  - Myelodysplasia
- Lymphomas
  - Hodgkin disease
  - Non-Hodgkin lymphoma
- Multiple myeloma
- Myeloproliferative neoplasms
  - Myelofibrosis
  - Polycythemia vera
  - Myelofibrosis
  - Chronic myelogenous leukemia
- Solid tumors
  - Neuroblastoma
  - Desmoplastic small round cell tumor
  - Ewing sarcoma
  - Choriocarcinoma

whether or not they will be transplanted into the donor. The use of extensive cytotoxic treatment, as well as intense or advanced-stage malignancy also precludes the harvesting of blood or bone marrow.Only HLA-matched unrelated donors may be used for allogenic transplants. However, the number of HLA-matched unrelated donors is only around 30% of the population. [17] Patients who are not part of a sibling group have a 30-40% to 40% chance of finding a blood-related donor through registries. Transplants of cord blood from HSC have improved the chances of being effective for pediatric and adult patients.

The recovery of stem cells is particularly supported by autologous, syngeneic, or allogeneic after myelosuric therapy for non-malignant diseases.Heterotropic cells are used for acquired blood stem cell (eg, aplasia) and correction of congenital problems (lack of bone marrow) (eg, thalassemia and severe combined immunodeficiency syndrome). [18]

TYPES OF GRAFTS

Some of the most common treatments for various types of cancer, such as chemotherapy and radiation, are cytotoxic to the bone marrow. At higher doses, the marrow is affected in general. The mainstay of stem cell therapy uses high doses of chemo or radiation to destroy the cancer cells which may be immune to lower doses of the rest.You must have a good supply of stem cells before the treatment starts. the transplanted cells then begin to re-establish the bone marrow's output of blood cells In certain settings, lower doses of radiation or chemotherapy that don't completely kill the bone marrow can be used.

The cells that will be transplanted can be taken from the bone marrow (called a bone marrow harvest), from the bloodstream (called a peripheral blood stem cell collection, which requires that you take medication to boost the number of hematopoietic stem cells in the blood), or occasionally from blood obtained from the umbilical cord after the birth of a normal newborn (which are stored in umbilical cord blood banks).

There are two main types of hematopoietic cell transplantation: autologous and allogeneic.

a. Autologous

   Autologous HSCT requires the extraction (apheresis) of haematopoietic stem cells (HSC) from the patient and storage of the harvested cells in a freezer. The patient is then treated with high dose chemotherapy with or without radiotherapy with the intention of eradicating the patient's malignant cell population the cost of partial or complete bone marrow ablation (destruction of patients bone marrow function to grow new blood cells). The patient’s own stored stem cells are then returned to his/her body, where they destroyedtissue and resume the patient's normal blood cell production.

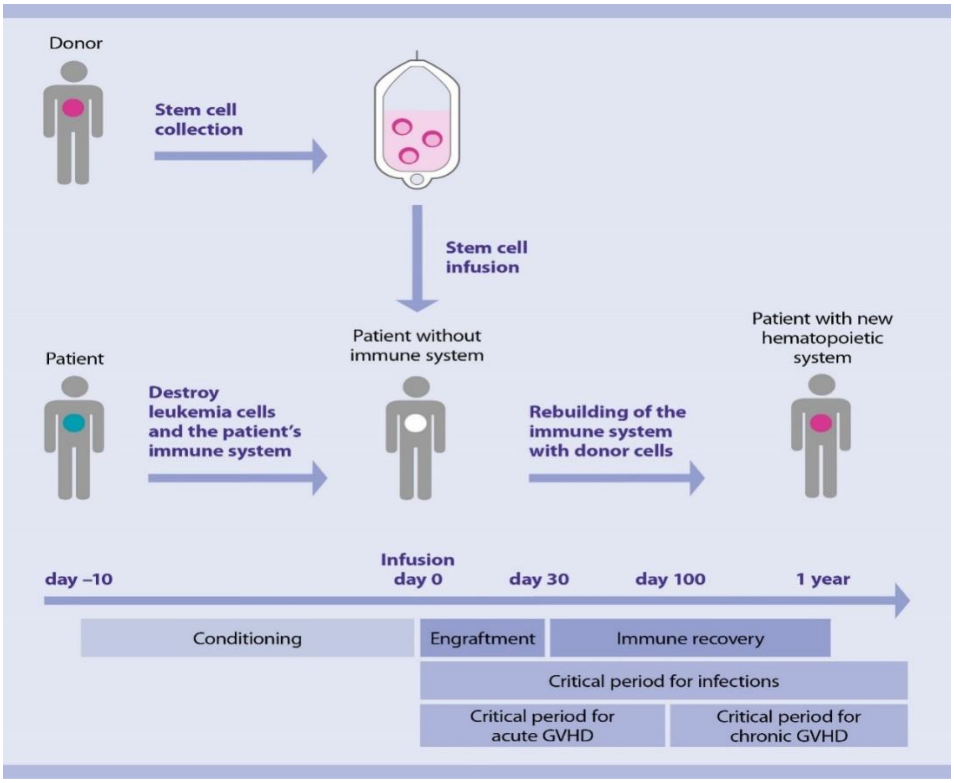

Figure-3: Autologous Stem Cell Transplantation

Autologous transplants have the advantage of lower risk of infection during the immune- compromised portion of the treatment since the recovery of immune function is rapid. Also, the incidence of patients experiencing rejection (graft-versus-host disease) is very rare due to the donor and recipient being the same individual.

These advantages have established autologous HSCT as one of the t standard second –line treatments for such diseases as lymphoma. However for others such as Acute Myeloid Leukemia, the reduced mortality of the autogenous relative to allogeneic HSCT may be outweighed by increased likelihood of cancer relapse and related mortality, and therefore the allogeneic treatment may be preferred for those conditions. Researchers have conducted small studies using non-myeloablative hematopoietic stem cell.

b. Allogeneic transplant

Allogeneic HSCT involves two people: the (healthy) donor and the (patient) recipient. Allogeneic HSC donors mustmust have a (tissue) type that matches the recipient. Matching isperformed on the basis of variability at three or more loci of theHLA gene, and a perfect match at these loci is preferred. Even ifThere is a good match at these critical alleles, the recipient willRequire immunosuppressive medications to mitigate graft-versus-host disease, allogeneic transplant donors may be related (usually a closely HLA matched sibling), syngeneic (a monozygotic or'identical' twin of flue patient - necessarily extremely rare since fewpatients have an rim identical twin, but offering a source of perfectly.

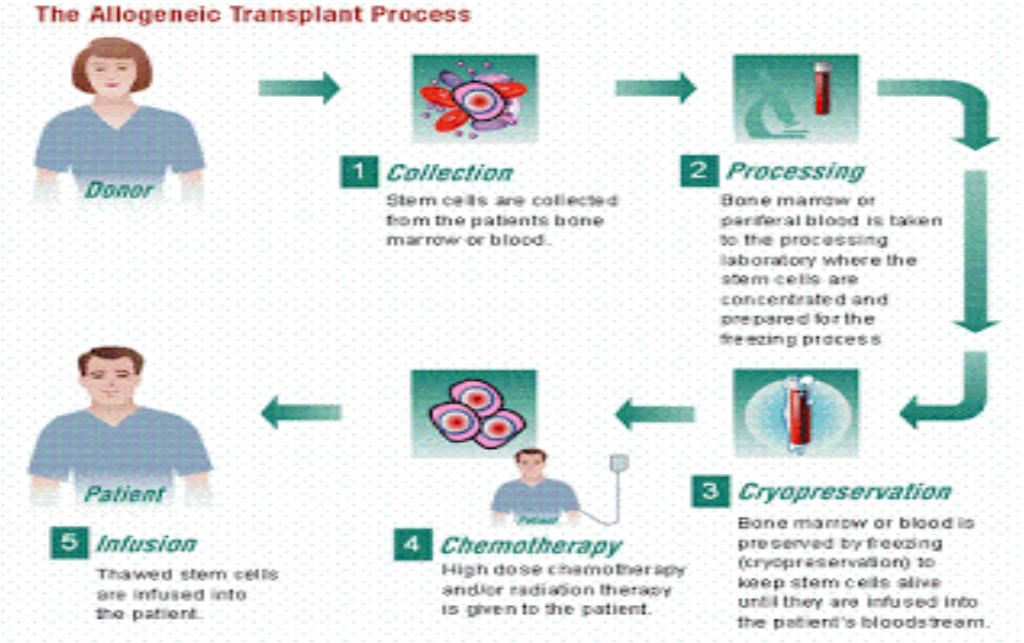

Figure-4: Allogeneic stern cell transplantation

Allogeneic transplants are also performed using umbilical cord blood as source of stem cells. In general, by transplanting healthy stem cells to the recipient's immune system, allogeneic HSCTs appear to improve chances for cure or long –term remission once the immediate transplant-related complications are resolved.

A compatible donor is found by doing additional HLA-testing From the blood of potential donors. The HLA genes fall in two categories (Type I and Type II). In general, mismatches of the Type I genes (i.e. HLA-A, HLA-B, or HLA-C) increase the risk of graft rejection. A mismatch of an HLA Type II gene (i.e. HLA- DR, or HLA-DQB1) increases the risk of graft-versus-host disease. In addition a genetic mismatch as small as a single DNA base pair is significant so perfect matches require knowledge of the exact DNA sequence of these genes for both donor and recipients.

PREPARATIVE REGIMENS

The aim of myeloblastic therapy before transplantation is to remove cancer, and to induce immunosuppression that helps with engraftment. Additionally, the preparative regimen will improve the antitumor immune response by depletes tumor cells, which triggers a spillover of tumor antigens into the antigen-presenting cells. The increased cell proliferation associated with increased T-cell activity may lead to cytotoxic or cytostatic activity. [19]Irradiation is myelotoxic and immunosuppressive, is not related to resistance to medication, and targets noncancerous tissues, too. The results of total-body irradiation are not dependent on the blood supply, and organ boosting is definitely possible.

Delivering a decreased dose of total body irradiation to fractions of the patient is more effective and less harmful total-body irradiation and cyclophosphamide fractionation have been the key modes of therapy since the 1980s total-body irradiation doses were found to be higher than expected but survival was lower among recipients of transplant recipients.the treatment of leukemias uses radiolabeled monoclonal antibodies that target antigens Selective radiation offers improved precision. [20]

Regiments using whole-body irradiation have been established as a result of the

toxicological concerns and radiation scarcity. Acute myeloid leukemia could be treated with busulfan and cyclophamide in the early stages by that year in 1983.To minimize toxicity, the dosage of cyclophosphamide was soon reduced. Most of the side effects occur with high busulfone and its metabolites.Lowering the toxicity by changing the busulfan dosage according to plasma levels of the drug or administering it intravenously. [21]

A better understanding of graft-versus-tumor biology led to the development of reduced-intensity preparative regimens in the late 1990s. Unlike traditional myeloablative preparations, these regimens are primarily immunosuppressive and depend on the graft to eradicate cancer. If immunologic elimination of malignant stem cells is the key to successful allotransplantation, then reduced-intensity regimens seem preferable.

COMPLICATIONS

Early Effects

Hematopocele is a frequent complication of marrow transplantation. The most common hematologic side effect of myeloid, methotrexate, and allo-regimens are anemia (used to prevent GVHD). In the glottic zone, oropharyngeal mucosa may be painful and require intubation. Nausea can be caused by the intestinal mucosa. Diarrhea and a lack of nutrients can be caused by the gastrointestinal mucosa. The keratinocyte growth factor decreases the risk of the recurrence of oral mucositis post-transplantation. [22]

The second most common acute adverse effect is a potentially fatal syndrome of painful hepatomegaly, jaundice, and fluid retention, traditionally called hepatic veno-occlusive disease. However, the term “sinusoidal obstruction syndrome” is more accurate because damaged sinusoidal endothelium sloughs and then obstructs the hepatic circulation, injuring centrilobular hepatocytes. In severe sinusoidal obstruction syndrome, renal and respiratory failure may occur.

Delayed Effects

Most transplant patients remain active and stable, but long-term complications, such as chronic GVHD are to be expected. The risk increases with the recipient's age and is increased because they are blood dependent donors. Chronic GVHD is often associated with self-tolerance and is almost always followed by scleroderma or Sjgren syndrome. Chronic GVHD can cause bronchitis, sicca, esophagealititis, keratoconjunct, and immune suppression. Corticosteroids treatment may be needed for at least two years. Corticosteroids can lead to aseptic necrosis of bone and osteoporosis, and therefore might predispose the patient to fatal infections. Extreme hypogammaglumlia can be treated with intravenous immune globulins.

Future of Hematopoietic Stem-Cell Transplantation:

In the past few years, there has been a renewed interest in discovering ways to minimize the risk of relapse. It's very exciting to note that new approaches to controlling GVHD during allogene HSCT are in development. This is primarily ascribed to donor T cell activity directed toward relapsed or residual leukemic cells as well as well as NK and B cell activity. currently being studied in clinical trials are stem cell transplantation techniques, vaccines against TAA, monoclonal antibodies, and targeted cellular immunotherapy.

CONCLUSION

Embryonic stem cells can give rise to hematopo cells. Compatibility problems can be solved by extensive banked stem-cell lines or individually. Using embryonic stem cells can save HLA typing and selection of hematopic stem cells, and sometimes even prevent it from being necessary.

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