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Overview of hematopoietic stem cell transplantation

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Abstract

Hematopoietic stem cell transplantation (HSCT) is the intravenous administration of hematopoietic stem cells (HSC) to restore blood cell production in individuals whose bone marrow or immune system is damaged or dysfunctional. This approach has been used to treat various malignant and nonmalignant disorders for the past half-century.

HSCT is performed in two ways, autologous and allogeneic. In the clinic, the type of stem cell transplant is decided according to the patient's diagnosis. Both kinds of transplantation have advantages as well as disadvantages. Knowing and managing the HSCT process well affects the success of the transplant. Knowing the complications that may occur after transplantation will facilitate the patient's treatment process. In this short review, the HSCT process has been tried to be explained with general titles.

Keywords: hematopoietic stem cell transplantation (HSCT), stem cell (SC), human leukocyte antigen (HLA), graft versus host disease (GVHD).

1. Introduction

1.1. What is Hematopoietic Stem Cell?

HSCs are cells found in bone marrow (BM), peripheral blood (PB), and umbilical cord blood (UCB) that can self-renew and differentiate into all adult blood cell types (Fig. 1). The spongy BM contains HSCs. In the bone marrow, HSCs create cells of the myeloid and lymphoid lineages, which are essential components of the immune system. The lymphopoiesis begins in the lymphoid series, and T, B, and natural killer (NK) cells, which are components of innate and adaptive immune cells, are created. The myeloid series gives rise to other blood cell components. Characterization of HSCs in clinical and research laboratories is done using CD markers. The existence and definition of HSCs were made 50 years ago, and studies on HSCs are still ongoing (1–3).

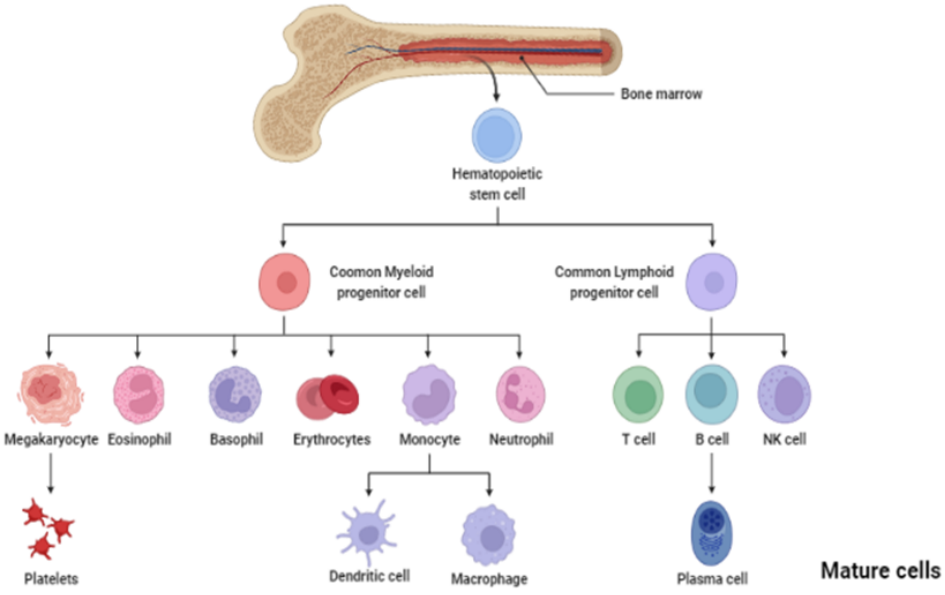

Fig. 1. Scheme of formation of mature blood cells from HSCs. Mature blood cells are formed from the blood-forming HSCs in the BM. Stem cells (SCs) are characterized by antigens on their surface (immunophenotyping)

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1.2. Hematopoietic Stem Cell Transplantation

Bone marrow transplantation, also known as HSCT, involves the transfer of healthy HSCs to patients with damaged bone marrow (4). In recent years, HSCT has entered the clinic as a life-saving treatment for many diseases, including autoimmune and genetic diseases, especially malignant and non-malignant hematological cancers. Since the 1940s, many developments have been recorded in the field of stem cell transplantation (SCT). Today, HSCT, which is accepted by many authorities to be used especially in treating hematological diseases, is performed in three different ways. They are allogeneic (from siblings, relatives, and HLA-matched unrelated donors), autologous (use of patient's own SCs in solid tumors), and syngeneic (from twin siblings). HSCs are derived from BM, PB, and UCB (5).

1.3. Autologous Stem Cell Transplantation

Using the patient's own SCs for transplantation is the main focus of autologous SCT. To increase the number of SCs in the peripheral blood, either cytokine (granulocyte colony-stimulating factor (G-CSF)) or cytotoxic agents in combination with cytokine are given to the patient as a mobilization agent to allow the SCs to leave the BM and enter the PB. Plerixafor, a CXCR4 antagonist, is a highly potent mobilizing agent. The primary function of G-CSF in this context is to trigger the release of proteolytic enzymes, particularly metalloproteinase-9, from BM stromal cells, allowing HSCs to be separated from the stroma. The presence of a sufficient number of SCs in the patient's PB is referred to as mobilization, and it is measured using a flow cytometer and the CD34+ cell surface antigen. The patients' apheresis process begins when they achieve a suitable amount of SCs in the calculation made using the CD34+ SC count and the patient's white blood cell count. The apheresis equipment collects SCs from the patient, freezes them under specific circumstances, and stores them in liquid nitrogen tanks until the transplantation procedure. A series of high-dose chemotherapy and radiotherapy are administered to the patient to kill the blasts identified as undesirable cells. Following that, similar to a blood transfusion, healthy SCs are delivered to the patient on the day of transplantation (Fig.2). For the treatment of Hodgkin Lymphoma (HL), Non-Hodgkin Lymphoma (NHL), and Multiple Myeloma (MM), autologous transplantation is often favored (MM). The patient's hematopoiesis flow is regulated by SCs reinfused into the patient. This process, in which healthy blood cell production begins again, is called engraftment. This procedure is monitored by the daily blood counts of transplant recipients. Although the incidence of problems following transplantation is lower than allogeneic transplantation, the risk of illness recurrence is considerable. Because autologous transplantation uses the patient's own SCs, graft failure (the inability of the transplanted cells to grow and divide in the BM) is uncommon, and graft versus host disease (GVHD), which occurs in allogeneic transplantation and is extremely difficult to treat, is not seen (6).

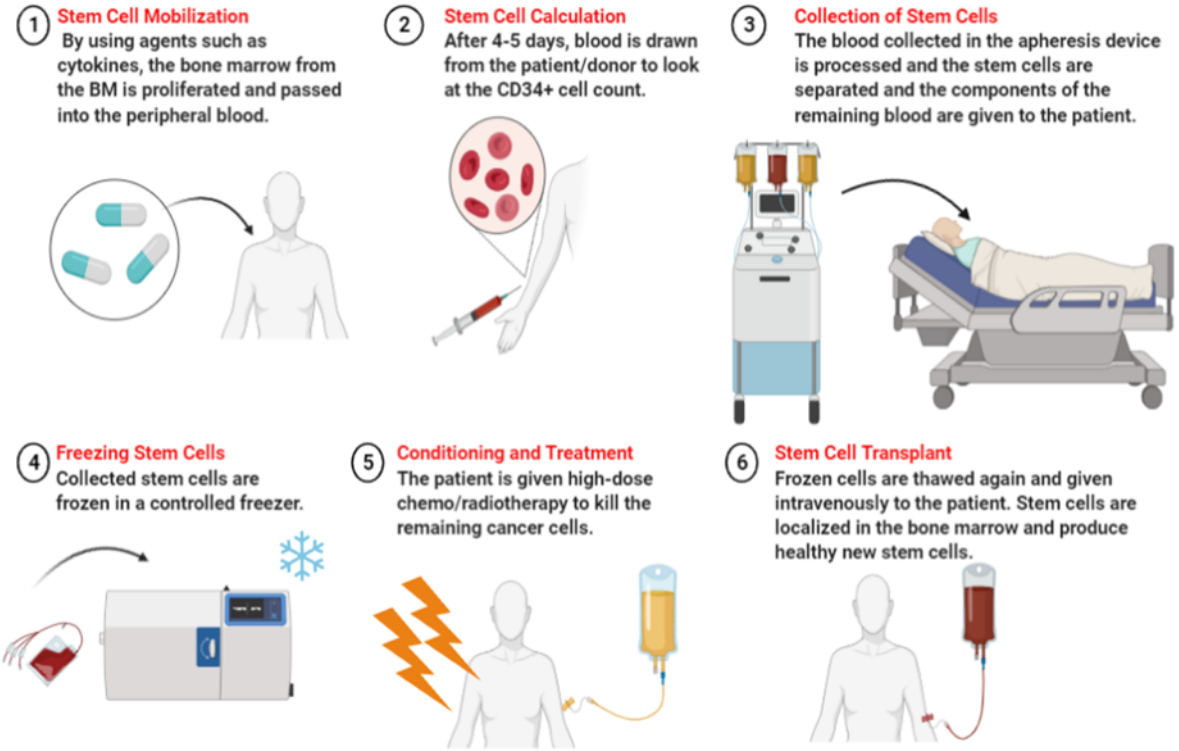

Fig. 2. Autologous SCT process

1.4. Allogeneic Stem Cell Transplantation

Patients with malignant and non-malignant hematological blood disorders are treated with allogeneic SCT when autologous SCT is not possible. In this type of transplant, human leukocyte antigen (HLA) compatibility between the patient and the donor is critical. Acute Myeloid Leukemia

(AML), Acute Lymphoblastic Leukemia (ALL), Chronic Myeloid Leukemia (CML), Chronic Lymphocytic Leukemia (CLL), Multiple Myeloma (MM), Non-Hodgkin Lymphoma (NHL), and anemia are all treated with allogeneic SCT (3).

1.4.1Types of Allogeneic Stem Cell Transplantation

Twins undergo *syngeneic SCT.* The community has a low rate of identical twins. The main benefits of syngeneic SCT are the minimal risk of developing GVHD and the lack of graft rejection risk. Because of these factors, the patient is not receiving long-term immunosuppressive medication (7).

Haploidentical SCT is performed on at least 50% HLA-matched relatives. The likelihood of graft rejection and GVHD is significant, depending on the degree of HLA incompatibility. Furthermore, after this transplant, the immune system takes a long time to rebuild (8).

Sibling SCT is a form of transplantation between siblings. Because of the genetic compatibility in HLA, it is frequently preferred. Transplantation from HLA-matched siblings is the clinic's first choice.

Unrelated SCT is an allogeneic SCT performed between individuals with unrelated HLA matching. When there are no HLA-matched family members, this is the transplant method of choice.

1.5. Sources of Hematopoietic Stem Cells

BM, PB, and UCR are the SC sources used for autologous or allogeneic HSCT. The BM source collects BM from the donor via aspiration while the donor is under general anesthesia. Using specific biopsy needles, BM is carefully aspirated from the posterior iliac crest region under operating room circumstances. The donor may undergo bleeding, infection, and localized pain throughout the 2.5-hour operation. Patients and donors who choose to collect SCs from bone marrow are subjected to a thorough physical assessment and any relevant tests. The patient does not need to introduce a specific catheter in BM transplants, and SCs are collected in one go under surgical settings. Another advantage is that no agents, such as G-CSF, are required, as with peripheral SC sources. On the other hand, the engraftment of neutrophils and platelets happens more slowly. Because of their quick engraftment timeframes and numerous other advantages, PB-derived SCs are the most often used source of HSCT in clinics. The quantity of SCs in the PB is normally modest. G-CSF and plerixafor are utilized to proliferate and transport SCs from the BM to the peripheral circulation. If sufficient CD34+SCs (5 to 15 g/kg/day) are calculated 4-5 days following the use of drugs, SCs are harvested from patients or donors in the apheresis unit. Because the veins of some patients or donors (children, patients undergoing continuous intravenous therapy, etc.) are insufficient for collecting enough SCs, the collection is done via a central venous catheter. Because not enough stem cells can be harvested in one go, SC collection (apheresis) may continue for a few days. In addition to being simple and inexpensive, acquiring PB-derived SCs has several drawbacks. The patient or donor may experience bone discomfort and flu-like symptoms using mobilization agents. Furthermore, citrate or anticoagulant chemicals used to prevent coagulation in apheresis unit sets may produce unwanted effects on the patient or donor (hypocalcemia). Another concern is the possibility of central venous catheter bleeding and infection. However, compared to BM, the recovery of all of these adverse effects occurs concisely.

The chord is constricted from a certain point after the infant is born to collect SCs from the UCB. CB is contained in a sterile blood bag with the anticoagulant. It is extracted from erythrocytes and plasma and frozen for future transplantation. Because HLA type is not an issue with UCB transplants, the risk of GVHD is lower than in other sources. The most extended engraftment timeframes are caused by the low quantity of stem cells (CD34+) derived from UCB. At least stem cells (CD34+) are isolated from cord blood using the above procedures. PBSCs produce the most significant number of stem cells. However, the danger of GVHD, the most common issue in allogeneic transplants, is substantial in all three donors. These sources of SCs contain GVHD-inducing T lymphocytes. The ratios of lymphocytes, monocytes, T cells, and dendritic cells are very high in PBSCs (9,10).

1.6. Steps of HSCT;

1.6.1. Preparation Regime: The patient is first readied for travel at this stage by employing particular preparation regimens. The preparation regimen is based on the use of chemotherapy, radiation, and other biological treatment procedures for antineoplastic or immunosuppressive reasons before autologous and allogeneic transplantation. These treatments, typically including high-dose chemotherapy, significantly contribute to the pulmonary problems reported following transplantation. Because there would be no genetic variations in autologous transplants, the goal of the preparation regimen is to remove the patient's undesirable cells and tumors. When SCs from the donor (relative-unrelated) are given to the patient in allogeneic SCs, a response may develop due to differences in HLA tissue compatibility. Priming regimens reduce the patient's immune system to prevent the transplant rejection reaction. Furthermore, the patient's defective hematopoiesis is removed using the preparation regimen used before allogeneic SCT (myeloablation). Preparation regimens are chosen in various centers by parameters such as patient diagnosis, condition, other illness factors, and transplant-related mortality risk (11–13)

1.6.2. Allogeneic Transplant Donor Selection: Allogeneic HSCT is the preferred treatment for a wide range of malignant and non-malignant disorders. Because the purpose of allogeneic HSCT is to replace the patient's ineffectively functioning hematopoiesis with that of a donor, so finding a compatible donor is a prerequisite. It is a time-consuming and complex process for both recipients and donors (10). Donor selection is crucial for allogeneic-HSCT success. When

making this decision, both relatives and non-relatives are considered. Tissue typing of fathers, mothers, siblings, and other relatives looks at the donor and recipient's HLA. When there is HLA compatibility, a stem cell source, and several donors available, donor age, gender, sex factor, weight, ABO blood group, and virus serological status should be evaluated in the donor selection process (8).

The phases of selecting a suitable donor in allogeneic SCT can be summarized as follows:

1. The tissue type of the patients is determined.

2. Family members' tissue type is determined (transplantation process starts at appropriate HLA match)

3. If compatible tissue typing cannot be established in family members, SCT centers apply to institutes that maintain national and international donor databases in search of suitable donors (National Marrow Donor Program (NMDP), German Bone Marrow Donor Center (DKMS), Turkish Stem Cell Coordination Center (TÜRKÖK), etc.)

4. Following the completion of the necessary procedures, the SCs are harvested from the compatible donor and sent to the transplant center under appropriate conditions (13).

1.6.2.1 Human Leukocyte Antigens (HLA)

Tissue typing (HLA screening) should be performed by experts in accredited laboratories as soon as possible when it is decided to perform allogeneic SCT for the patient. The HLA system is found on chromosome 6's short arm (6p21.3) and contains the most polymorphic gene cluster in the whole human genome. HLA system allows our immune system to recognize non-self. HLA is evaluated in the laboratory using molecular methods to determine whether there is tissue compatibility between the recipient and donor in allogeneic HSCT. Our HLA type is passed down from our parents. As a result, relative (family) screening is initiated first in the hunt for a donor. The HLA complex comprises Class I, Class II, and Class III sections and is found on the short arm of the sixth chromosome. HSCT screens for Class I genes HLA-A, B, and C and Class II genes HLA-DR, DQ, and DP. Donors should be entirely compatible in inbred screening and have an HLA match of 6/6 or 10/10 in unrelated screening. There is a 3/6 or 5/10 concordance in cases of one or two antigen mismatches or haploidentical cases (10,13–15).

1.6.3. Harvesting and Storage of Stem Cells from Peripheral / Bone Marrow

Under general anesthesia, BMSCs are extracted from the pelvis bone. Special bone needles used in BM extraction are inserted with injectors into multiple sections of the bone, and roughly 5 ml of BM is aspirated so that it does not mix with blood. Heparin (5,000 U/mL) must be used to clean injectors with used bone needles. To avoid coagulation, the aspirated BM contains ACD anticoagulant solution and is collected in unique bags. According to popular belief, 2 -3 x10^8 nucleated cells/kg are collected. The obtained BM is given to the patient the same day or the following day (16).

PBSCs are typically detected in tiny numbers. The number of PBSCs is enhanced approximately 100 times by utilizing different chemotherapeutic and growth agents (G-CSF, GM-CSF) (17). When sufficient SCs are obtained, they are harvested using special machines in the apheresis unit. If the harvested SCs are to be administered to the patient within 72 hours, they can be kept in the refrigerator at 2-8 °C. If the storage time is more than 72 hours, the SCs must be frozen to maintain viability. To prevent cellular dehydration and the production of ice crystals in the cells, 5-10% dimethyl sulfoxide (DMSO) is given to the collected SCs after centrifugation. Mechanical freezers (≤ -80°C) are used to freeze stem cells, which are then preserved in vapor-phase liquid nitrogen (≤−150°C) until the day of transplantation (6).

1.6.4. Transfusion of Stem Cells to the Patient

Frozen stem cell samples are thawed in a 37 °C water bath in the patient's room on the day of transplantation and infused immediately. Most adverse reactions during SCT are due to DMSO, fragmented granulocytes, or ABO incompatibility. Mild reactions such as nausea, vomiting, abdominal cramps, cough, hypertension, hypotension, and sometimes cardiac symptoms can be observed during SCT (Figure 2) (6).

1.7. Factors Affecting Transplant Success and Complications After Transplantation

Numerous factors influence transplant success. These factors may be related to the disease (disease resistance, disease phase, clonal abnormalities, and so on in malignancies, and the type of disease and associated rejection risk in non-malignant diseases), as well as the patient himself (age, comorbidities, infectious diseases/colonization, and so on). Furthermore, donor-related difficulties and SC sources can impact disease control and transplant-related mortality (18).

Another critical aspect is the occurrence of adverse responses and problems following transplantation. Despite advances in research and technology, severe and fatal reactions to drugs used in recipients' pre-transplantation preparation regimens, GVHD developing after allogeneic transplantation, infections resulting from recipient immune suppression, and respiratory failure in some patients are significant complications (12).

Post-transplant infections are one of the most serious of these problems. Cytomegalovirus (CMV) infection is one of the most prevalent after allogeneic transplantation. CMV infection can induce fever or cytopenia in patients, as well as pneumonia, hepatitis, gastroenteritis, retinitis, and encephalitis. CMV infection and the immune system both occur concurrently. For example, whereas GVHD disease increases the likelihood of CMV infection, CMV infection may have a role in the development of GVHD. The protein level in the patient's sample (plasma, urine, serum, tissue, etc.) or DNA using polymerase chain reaction is used to determine CMV (PCR). Although numerous factors influence CMV treatment,

antiviral medications, high-dose immune globulin therapy, and particular T cells are employed (19).

GVHD is one of the most prevalent problems following allogeneic SCT. GVHD, which is extremely difficult to treat, is studied in acute and chronic stages. It is referred to as acute GVHD if it occurs during the first 100 days of HPSCT and chronic GVHD if it occurs after 100 days. Age of the patient and donor, female donor option, unrelated donor option, and, as previously indicated, the presence of CMV in the patient or donor are all factors that contribute to the emergence of GVHD. The reactivity of the donor's T cells as a result of seeing the patient's tissues as antigenically foreign is critical in GVHD illness. GVHD causes serious harm to the patient's skin (scaling), liver (change in bilirubin level), and digestive system (severe diarrhea). The severity of GVHD and the extent of organ damage it produces are closely proportional to the level of HLA incompatibility (20).

1.2 Stem Cell Transplantation in Turkey

The journey of SCT in Turkey began in 1978. Prof.Dr.Korkut Zerkan performed the first allogeneic BMT in Turkey at Hacettepe University Medical Faculty Hospital in 1978, and Prof.Dr. Onder Berk and his colleagues performed the first autologous BMT at Gülhane Military Medical Academy in 1984. In 1992, the first autologous PBHSCT was conducted. Prof.Dr. Gündüz Gedikolu and Prof.Dr. Made by Sema Anak completed the first SCT in pediatric instances. Dr. Atila Tanyeli performed the first pediatric autologous SCT on a patient with recurrent HL in 1992 (21).

At the current level, Turkey competes with European countries on HSCT. Turkey, which has attained world standards due to qualified professionals trained in developing technical infrastructures, offers more appropriate and quality treatment options than other European countries and the USA. With the rise of health tourism, people worldwide are flocking to Turkey for transplants. The number of patients seeking transplantation services grows in lockstep with the expansion of stem cell transplantation centers. Of course, establishing the Turkish Stem Cell Coordination Center (TÜRKÖK) under the Ministry of Health to encourage unrelated SC donations and construct a donor database pool was critical to this accomplishment.

HSCT is a safe form of therapy for the treatment of hematological diseases. Having information about the transplant types will enable the selection of the right transplant type. It is very important in the search for alternative donors and HLA-matched allogeneic transplants. Technological developments to prevent complications that may occur after transplantation will further increase the use and effectiveness of HSCT.

Conflict of interest

The authors declared no conflict of interest.

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Authors' contributions

Concept: N.M., Design: N.M., Data Collection or Processing: N.M., Analysis or Interpretation: N.M., Literature Search: N.M., Writing: N.M.

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