



## Hematopoietic stem cell transplantation in children

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### Abstract

Bone marrow transplantation is now called hematopoietic stem cell transplantation (HSCT) because, apart from bone marrow, peripheral blood and umbilical cord blood can also be used as stem cell sources. HSCT can be performed in three ways. One is autologous stem cell transplantation. The other is allogeneic stem cell transplantation. Another type of transplantation applied in recent years is haploidentical transplantation. More than 20% of all allogeneic HSCTs are performed in patients under 20 years of age. HSCT has become a well-established lifesaving treatment procedure for many patients with hematological malignancies, hemoglobinopathies, inborn errors, or bone marrow failure syndromes. HSCT is now integrated as an essential part in many treatment concepts and protocols. HSCT is a treatment that provides an increase on success compared to other treatments when it is performed in suitable patients and in accordance with the standards. Selection of the appropriate transplant type, appropriate donor, appropriate preparation regimen, and close monitoring of complications are essential.

**Keywords:** hematopoietic stem cell transplantation, child, indication, graft versus host disease

### 1. Introduction

Bone marrow transplantation is now called hematopoietic stem cell transplantation (HSCT) because, apart from bone marrow, peripheral blood and umbilical cord blood can also be used as stem cell sources (1, 2).

HSCT can be performed in three ways. One is autologous stem cell transplantation. It is the freezing of stem cells taken from the patient and giving them to him after high-dose chemotherapy. In this way, in many malignant diseases, intense chemotherapy can be given to cause severe myelotoxicity and cure can be provided. The myelotoxicity problem is solved by the proliferation of the stem cells given to the patient in the bone marrow. The stem cell source may be bone marrow or peripheral blood. It is frequently used for multiple myeloma in adults and solid tumors in children (1, 2).

The other is allogeneic stem cell transplantation. Stem cells that are fully suitable or 9/10 suitable for human leukocyte antigens (HLA) tissue antigens are collected from another person and given to the patient. First, the relatives of the patients are screened for HLA antigen compatibility. If there is no suitable relative, the bone marrow bank is applied to the unrelated donors for screening. The source of stem cells can be bone marrow, peripheral blood, or cord blood. Chemotherapy or radiotherapy should be given before the patient is given stem cells. With this application, which is called the preparation regime, the cells in the bone marrow are cleaned, space is opened for new stem cells to be given, cancer cells, if any, are also cleaned, and immune suppression

is applied to prevent the harm that the given stem cells can cause to the patient. It is frequently used in hematological malignant diseases, hemoglobinopathies, and metabolic diseases (1, 2).

Another type of transplantation applied in recent years is haploidentical transplantation. If stem cell transplantation is required in patients who do not have a complete or nearly complete HLA match, stem cells are collected from two or more antigen-incompatible individuals. The probability of finding a donor in these transplants is high. However, the probability of severe graft versus host disease (GVHD) is very high due to inappropriate antigens. Haploidentical stem cell transplantation is indicated in patients whose only treatment is stem cell transplantation, but who do not have a suitable donor (1, 2).

The HSCT stages are; preparative regimen (starting from day -10 or -7), stem cell infusion (day 0), engraftment; often +10 to +20 days (for neutrophils; the first day when the neutrophil count is  $0.5 \times 10^6/L$  for 3 consecutive days, for platelets; the first day without platelet suspension for a week), chimerism monitoring, GVHD monitoring, monitoring for possible side effects and infections.

Chimerism should be followed up after engraftment in allogeneic or haploidentical HSCT. It shows sensitively whether the leukocytes produced are of patient or donor origin. The most widely used and accepted method today is the determination of short repeat sequences by polymerase chain reaction, and its sensitivity is 1-3%. Sensitivity can be increased (<1%) with chimerism testing in specific cell lines.

Peripheral blood cells are sufficient for chimerism measurement. Bone marrow samples can be used to evaluate recurrences early in patients with acute leukemia. Patients at high risk of graft rejection, recurrence in malignant diseases, and development of graft versus host disease can be identified using serial chimerism determinations, and this information can be used to guide the initiation and timing of necessary applications (increasing, decreasing, terminating immunosuppressive, donor lymphocyte infusion, and so on) (1, 2).

More than 20% of all allogeneic HSCTs are performed in patients under 20 years of age. HSCT has become a well-established lifesaving treatment procedure for many patients with hematological malignancies, hemoglobinopathies, inborn errors, or bone marrow failure syndromes. HSCT is now integrated as an essential part in many treatment concepts and protocols (1, 2).

The first successful stem cell transplantation application in history started in 1952 with a case diagnosed with acute leukemia, for this reason E. Donnall Thomas was awarded the Nobel Prize in 1990 (3). HSCT indications and applications have changed significantly in the last 20 years. Developing sources of hematopoietic stem cells, less toxic conditioning regimens, and successes in graft versus host disease prophylaxis and treatment have led to the application of hematopoietic stem cell transplantation in increasing numbers from malignant to nonmalignant.

#### **Indications for HSCT in children**

The indications for HSCT in children recommended by the European Blood and Bone Marrow Transplantation Group (EBMT) are based on current clinical practices in Europe and America (1, 2).

It is essential to perform HSCT on the right patient at the right time, with the right steps. It is necessary to start by evaluating patient-related factors and disease-related factors separately when making a decision for transplantation in a patient.

It has been published as a guide by many transplant associations (EBMT, IBMTR) on which disease and when to transplant. There is an indication guide published by the Ministry of Health in Turkey, which is updated from time to time. The last update date is July 2017 (4). Guidelines show routine indications; standard treatment is left to clinical preference or not recommended. These guidelines are very important, but patient-related factors are at least as important as the indication when making the transplant decision. The length of the process, responsibilities in the process, continuous support, and organization should be explained to the patient and his family, and it should be stated that family support in this process will increase success.

In Turkey, 87.5% of the 6620 stem cell transplants performed in childhood are allogeneic HSCTs, and 53.5% of

these transplants were performed on non-malignant diseases, mostly on thalassemia major patients. In the malignant disease group, ALL is the most common followed by AML and other diseases (5).

#### **Acute Lymphoid Leukemia (ALL)**

HSCT is indicated in the high-risk group in ALL patients in first complete remission. Event-free survival is less than 50% in this group in most studies. A high-risk ALL group was defined in each chemotherapy protocol. The presence of some molecular and chromosomal anomalies and minimal residual disease positivity observed during certain periods of treatment are defined as high risk and HSCT is indicated. In ALL patients with early and very early bone marrow relapse, transplantation from an HLA-matched relative or unrelated donor is indicated.

#### **Acute Myeloid Leukemia (AML)**

In childhood AML cases, the cure rate is around 60% with intensive chemotherapy and intensive supportive care. Better outcomes have been reported for patients with good prognostic markers. HSCT is not recommended for these patients. HSCT is recommended in high-risk and very high-risk patients and in patients with relapse.

#### **Myelodysplastic syndrome, Juvenile myelomonocytic leukemia and Secondary leukemia**

Allogeneic HSCT from a suitable sibling or unrelated donor is recommended.

#### **Chronic Myeloid Leukemia (CML)**

Although allogeneic HSCT is the only curative therapy for CML patients, the introduction of specific tyrosine kinase inhibitors (TKI) has affected treatment strategies. If children in the chronic phase are in remission with TKIs, treatment can be continued for many years, and close molecular monitoring is required after discontinuation of treatment. There is insufficient evidence for treatment discontinuation. It may be necessary to start again. HSCT is recommended for patients in the chronic phase who cannot use different TKIs due to side effects or intolerance, or who cannot achieve remission despite using them. In the accelerated and blastic phase, HSCT is required.

#### **Hemoglobinopathies**

$\beta$ -Thalassemia and sickle cell anemia are the most common single gene diseases in the world. Although regular transfusion and chelation and supportive treatments such as hydroxyurea for sickle cell anemia significantly improve clinical findings and quality of life, it is not possible to exclude the disease and prevent treatment-related complications with these approaches. It is accepted today that HSCT is the only curative treatment in this patient group. We retrospectively enrolled 1469 patients with thalassemia major who underwent their first HSCT between 1988 and 2020 in

25 pediatric centers in Turkey. The median follow-up duration and transplant age were 62 months and 7 years, respectively; 113 patients had chronic graft versus host disease (GVHD). The 5-year overall survival, thalassemia-free survival, and thalassemia-GVHD-free survival rates were 92.3%, 82.1%, and 80.8%, respectively (6). The prognosis is much better, especially in cases of young age and in the low-risk group. For this reason, HSCT is recommended to be performed in early childhood before iron load and disease-related complications develop. In recent years, positive results have been reported in thalassemia with incompletely matched relative or compatible unrelated donor transplants. Recently, it has been reported that the rates of GVHD are low in cord blood transplants in  $\beta$  thalassemia and/or sickle cell diseases. However, graft failure and recurrence of the disease are still important problems for cord blood transplantation (7).

Currently, HSCT indications in sickle cell anemia in Turkey are limited, and it is indicated only in children with stroke, central nervous system complications, magnetic resonance imaging findings, or organ damage (4).

#### **Primary immunodeficiencies**

Allogeneic HSCT is currently the only accepted curative treatment for most immune deficiencies. Severe combined immune deficiency, various T cell deficiencies, Wiskott-Aldrich syndrome, leukocyte adhesion defect, chronic granulomatous disease, Chediak-Higashi syndrome, Griscelli syndrome, familial lymphohistiocytosis, X-linked lymphoproliferative disease can be counted in this group. If there is no HLA-matched family donor in this patient group, there is also an indication for transplantation from an unrelated donor (1, 2).

#### **Acquired severe aplastic anemia**

Transplantation is the first treatment option for severe aplastic anemia with compatible sibling donors. If there is no familial donor, immunosuppressive therapy including ATG and cyclosporine should be tried first. In cases unresponsive to this treatment, transplantation from an unrelated donor or cord blood is indicated (1, 2).

#### **Hereditary bone marrow failure syndromes**

Fanconi anemia is a rare genetic disease characterized by progressive bone marrow failure and a predisposition to malignancy, especially AML, accompanied by various bodily abnormalities. In Fanconi anemia cases, the only way to correct the hematological disorder is HSCT, and transplantation can be done from an HLA-matched sibling, relative or unrelated donor.

Diamond Blackfan Anemia is an inherited type of anemia characterized by the reduction or absence of erythroid precursors in the bone marrow. Allogeneic HSCT is indicated in cases with compatible sibling donors and unresponsive to steroids.

Amegakaryocytic thrombocytopenia is an autosomal recessive genetic disease that presents within days or weeks after birth. Allogeneic HSCT is the only curative treatment.

Congenital neutropenia is a disease characterized by severe neutropenia and severe bacterial infections from early childhood. In cases where patients do not respond to granulocyte colony-stimulating factor or develop MDS/AML, HSCT is indicated even if there is no matched family donor.

#### **Familial Hemophagocytic lymphohistiocytosis (HLH)**

The only curative treatment modality in familial HLH cases is allogeneic HSCT.

#### **Metabolic Diseases**

Metabolic diseases with an indication for transplantation are generally in the group of lysosomal storage diseases. It is based on the transfer of the missing enzyme from donor cells to the reticuloendothelial system and solid organs. Diseases with the most experience are adrenoleukodystrophy, type 1 mucopolysaccharidosis (Hurler's syndrome) and osteopetrosis.

#### **Solid tumors**

Data from the European Blood and Bone Marrow Transplant Group showed that transplantation prolongs the course in children with neuroblastoma and Ewing tumor. In other solid tumors, patients may benefit from autologous transplantation in the presence of some of the following special conditions (1,2):

Germ cell tumors: In the presence of relapse or progressive disease,

Soft tissue sarcoma: Stage 4 or after relapse with no chance of resection,

Wilm's tumor: In the presence of high-risk histology or relapse,

Brain tumors: Chemotherapy-responsive medulloblastoma or high-grade gliomas.

#### **Donor Selection for Pediatrics**

The outcome of HSCT depends in part on the matching between the donor and the recipient for HLA, encoded by a group of genes on chromosome 6; genes and products are labelled as the major histocompatibility complex. The HLA system is the most polymorphic genetic region known in the human genome. A set of HLA gene alleles, called haplotype, is inherited from each parent; therefore, the probability that a child inherits and shares both parental haplotypes with a full sibling is 25%. Such an HLA-identical sibling is still considered an optimal donor (8).

#### **Stem Cell Sources**

##### **1. Bone Marrow**

The classically accepted stem cell source for HSCT is bone

marrow. Multiple punctures of the iliac crest are performed in general anesthesia by experienced physicians and practitioners. The bone marrow is harvested by aspirations through adequately dimensioned needles. In very small children and if the iliac crest is anatomically not suitable for punctures, the aspirations could also be performed by punctures of the proximal tibia. The recommended number of nucleated cells for a successful "engraftment" is  $2-4 \times 10^8$  per recipient body weight. Although the application of granulocyte colony stimulating factor to increase the amount of stem cells in the bone marrow has been reported in adult donors, data on pediatric donors are very limited (8).

## 2. Peripheral Blood Stem Cell (PBSC)

The stem cell source preferred by many centers for autologous transplantation is peripheral stem cells. In recent years, PBSC has been used with increasing frequency in relative and even unrelated transplants from adult donors. Although there are reservations about donors, especially in the pediatric age group, there are publications in the literature reporting that the method is safe and the desired cell count can be easily reached. The greatest advantage of the use of peripheral blood stem cells is the shorter expected neutrophil and platelet engraftment times, resulting in fewer infectious problems, hospital stays and transfusion requirements. All of these factors directly affect the cost of transplantation. However, the collection process itself, particularly the difficulties in providing an appropriate venous route, the potential short- and long-term side effects of the drugs used in mobilization, and the increased risk of GVHD are the main considerations in the decision to use.

## 3. Cord Blood

The greatest advantage of cord blood is the low risk of viral transmission and GVHD. In addition, it can be used immediately without needing time for donor preparation, and it can be used with 1-2 HLA incompatibility, especially for cases with rare tissue group. The most restrictive factor regarding its use is the limited number of cells. The lowest acceptable cell counts are  $2.5 \times 10^7/\text{kg}$  for nucleated cells and  $1.7 \times 10^5/\text{kg}$  for CD34+ cells (8).

### Preparative (Conditioning) Regimens

The aim of the preparative regimen in HSCT is to prepare the patient for transplantation and has three separate components: "bone marrow clearance", "immunosuppression" and "disease eradication". Making room in the bone marrow is necessary for donor stem cells to reach the "niche" and "engraft". Rejection of the graft by recipient immune cells can be prevented by immunosuppression. Since the long-term course is related to disease control in malignancies, the main goal of the preparative regimen in this group is the eradication of the disease. The side effects of the preparative regimen are generally better tolerated in children than in adults, allowing for higher doses. On the other hand, total body irradiation

(TBI) regimens may cause late complications such as growth retardation, pubertal failure or delay, which is especially important for the pediatric age group. The most frequently used regimens in children are the regimens in which cyclophosphamide and busulfan are used together. Especially in congenital genetic diseases, different chemotherapeutic agents are added according to the underlying disease.

In order to reduce the side effects of the preparative regimens, reduced-intensity regimens have come to the fore. Fludarabine is the most commonly used basic agent in reduced-intensity protocols, and different agents are added according to the protocols (8).

### Stem Cell Cryopreservation

Stem cell cryopreservation should be processed and stored in accordance with the respective Medical Council, responsible local and overarching authorities as well as scientific society's guidelines (8). If necessary, collected cells can be stored for a maximum of up to 72 hours at  $2-6^\circ\text{C}$  before cryopreservation. However, cryopreservation within 48 hours or less is recommended to maintain the optimal viability of the cells. In the case of storage for  $>24$  h prior to cryopreservation, the maximum NC concentration should not exceed  $2 \times 10^8/\text{mL}$ . For cryopreservation, a number of different protocols are used worldwide. Usually, the maximum

acceptable NC concentration is  $\leq 4 \times 10^8/\text{mL}$ . If necessary, PBSC products can be diluted with autologous plasma or commercial resuspension medium. Increasing the cell concentration by volume depletion minimizes the number of cry stored bags needed, but the upper limit of the NC concentration needs to be considered. The final product includes 5–10% dimethyl sulfoxide (DMSO) as a cryoprotectant and 0.05–0.25 mL of ACD-A stabilizer solution per ml of transplant. It is recommended to freeze at a controlled rate of  $1-2^\circ\text{C}$  per minute. Cells need to be stored in vapor phase nitrogen at a temperature of  $\leq -140^\circ\text{C}$ . Cross-contamination while preparing and storing the cells must be prevented by taking appropriate measures.

At the time of autolog HSCT, cryopreserved bags must be thawed at the site of transplantation, and PBSCs should be reinfused within a maximum time span of 10–20 min of thawing using standard transfusion filters in order to minimize the detrimental effect of DMSO upon hematopoietic stem cells (HSCs). Previous washing for purposes of DMSO depletion is not routinely performed, as the loss and damage of HSCs are regarded as too high (8).

### Collection of HSCs in Children

Collecting or harvesting HSCs from children is a challenge, not only because children have different physiological and therefore anatomical situations but also because psychological, legal and ethical concerns in minors are sometimes more difficult compared to adult donors. In



addition, parents and/or legal guardians have to be addressed on all issues. The main difference to the adult setting is the small bodyweight; the difficulties in accessing venous access, especially in the leukapheresis setting; and the need for blood cell substitution in case of BM harvest. In children, the indications for autologous HSC harvesting are well-established. Using children in the allogeneic setting as donors is a completely different issue. Children should not donate HSCs if a comparable adult volunteer HSC donor is available, if the indication for the stem cell therapy is not first line, or if the therapy is experimental.

The main resources to harvest HSCs are BM and PBSCs. The basic techniques are quite similar to the techniques used in adults. For BM collection punctures of the iliac crests or in very small children, the tibia is used. For harvesting HSCs from the PB, leukapheresis is used with the same apheresis systems as in adults. To perform these procedures in children, physicians and nursing practitioners must have working knowledge about the normal age-dependent physiological parameters, like vital signs, growth, and psychological and motor development, and should be trained in the communication with children, parents, and/or their legal guardians (8).

### Transplant-Related Complications

High-dose radiotherapy and/or chemotherapy used in preparative regimens may affect all organs of the recipient and cause secondary effects of varying severity, either early or late. It is known that the development of complications may be associated with individual predisposition, immunosuppressive treatments, toxicities associated with pre-transplant treatments, and the presence of other concomitant factors during transplantation.

### Graft Versus Host Disease (GVHD)

GVHD is one of the most important complications of allogeneic transplantation. Although the risk is lower in pediatric cases than in adults, its frequency has increased, especially with the use of alternative donors.

In its simplest form, graft versus host disease occurs as a result of foreign recognition of recipient antigens by donor T cells. It is possible to classify them into two different groups: acute (aGVHD) and chronic (cGVHD). The time of onset is generally used to distinguish between acute and chronic, and those that develop before the first 100 days after transplantation are called acute, and those that begin later are called chronic. Occasional overlaps between the two groups suggest that this definition is not sufficiently deterministic. The clinical results of both are different and require different treatment methods on the basis of immunological differences. The most important risk factor is HLA incompatibility between donor and recipient, and the risk of GVHD increases as the mismatch rate increases. It has been reported that the risk of GVHD is increased in cases where peripheral blood is

used as the stem cell source, and the risk is lower in the use of cord blood. It has been reported that the frequency of Stage 3/4 aGVHD may be as high as 30-50% in non-relative transplants.

A significant improvement in GVHD rates was achieved by identifying 10 HLA loci at the allele level with the high-resolution method and selecting a more suitable donor. Other factors thought to be at risk for GVHD; high age of the recipient and donor, gender incompatibility, especially the recipient being male, the donor being a multiparous woman, the presence of malignant disease and the use of intensive preparative regimens.

The pathophysiology of acute GVHD is explained with three phase examples: tissue damage caused by the priming regimen, activation and proliferation of donor T cells, and damage to the recipient. Tissue damage caused by the priming regimen leads to the uncontrolled release of cytokines such as interferon- $\gamma$  (IFN $\gamma$ ), interleukin-1 (IL-1), and tumor necrosis factor- $\alpha$  (TNF $\alpha$ ). The release of these cytokines increases major histocompatibility complex expression in various tissues of the recipient and exacerbates the graft versus host activity of donor T cells. The small intestine and liver are particularly susceptible to organ damage caused by the myeloablative regimen. For this reason, it has been suggested that the risk of acute GVHD is higher in cases with intense diarrhea due to the preparative regimen. In the second step, the antigen presenting cells of the donor and recipient, together with inflammatory cytokines, stimulate the donor-derived T cells, causing them to proliferate and transform into effector cells. Stimulation of T cell proliferation initiates the third phase, and inflammatory cytokines such as IL-2, IFN $\gamma$  and TNF $\alpha$  released from T cells directly or indirectly cause tissue damage in the recipient. In addition to cytotoxic soluble vehicles, cellular cytotoxicity such as perforin-granzyme-B-mediated cytolysis and Fas-Fas ligand-mediated apoptosis also play an important role in the pathogenesis. This three-phase event results in specific clinical manifestations in which the skin, intestine, and liver are affected at different rates and can be graded according to their involvement rates (8).

Since graft versus host disease usually has a poor prognosis, preventive approaches to prevent its development are more important than treatment. Cyclosporin A, tacrolimus, mycophenolate mofetil, methotrexate and methyl prednisolone are used as preservatives.

The mortality rate is significantly lower in cases that show an early response to low-dose steroid therapy. However, cases without an early response should be evaluated in terms of other immunosuppressants without delay. New drugs, new monoclonal antibodies, complementary therapies, and immunomodulatory procedures such as intensive immunosuppression and extracorporeal photopheresis can provide remission, but the side effects of these treatments and especially infections are important problems that need to be

overcome. It may be possible to achieve immunotolerance with cellular therapies (mesenchymal stem cells) and it looks promising.

The pathophysiology of chronic (cGVHD) is not as well understood as the acute form. It is thought that both donor-derived alloreactive T cells, similar to aGVHD, and autoreactive T cell clones that cannot be deleted as a result of thymic damage. The main feature of many clinical findings in chronic (cGVHD) is extensive collagen deposition, and the clinical course often resembles autoimmune diseases.

#### Sinusoidal Obstruction Syndrome (SOS)

SOS, formerly called veno-occlusive disease of the liver (VOD), is the term used to designate the symptoms and signs that appear early after HSCT because of conditioning regimen-related hepatic toxicity.

The new EBMT Diagnostic Criteria for SOS in children are: (9)

No limitation for time of onset of SOSa

The presence of two or more of the followingb

- Unexplained consumptive and transfusion-refractory thrombocytopeniac
- Otherwise, unexplained weight gain on 3 consecutive days despite the use of diuretics or a weight gain >5% above baseline value
- Hepatomegaly (best if confirmed by imaging) above baseline valued
- Ascites (ideally confirmed by imaging) above baseline valuee
- Rising bilirubin from a baseline value on 3 consecutive days or  $\geq 2$  mg/dL within 72 h

aUp to 20% of children present late SOS

bWith the exclusion of other potential differential diagnoses

cWeight-adjusted platelet substitution/day to maintain institutional transfusion guidelines

dSuggested: imaging (US, CT, or MRI) immediately before HSCT to determine baseline value for both hepatomegaly and ascites

Defibrotide (1B): Despite the absence of randomized studies, it is the only agent approved by

FDA and EMA to treat severe SOS (>80% mortality).

#### Other Complications

Bacterial, fungal and viral systemic infections (cytomegalovirus, herpes virus, BK virus)

Mucositis

Lung complications

Pulmonary edema,

Bacterial, fungal and viral infections,

Idiopathic pneumonia syndrome

Diffuse alveolar hemorrhage

Kidney complications

Nephrotoxicity,

Hemolytic uremic syndrome-Thrombotic microangiopathy

Hemorrhagic cystitis

Heart complications

Cardiotoxicity,

Conduction disorders

Thrombosis within the catheter-connected heart

Endocrinological late complications

Hypothyroidism,

Adrenal insufficiency (due to steroid use),

Testicular or ovarian insufficiency,

Developmental delay

Secondary cancers

As a result, HSCT is a treatment that provides an increase in success compared to other treatments when it is performed on suitable patients and in accordance with the standards. Selection of the appropriate transplant type, appropriate donor, appropriate preparation regimen, and close monitoring of complications are essential.

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