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Invited Review

Hematopoetic stem cell transplantation in children

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Abstract

Bone marrow transplantation is called hematopoetic stem cell transplantation (HSCT), since peripheral blood and umbilical cord blood can also be used as sources of stem cell currently. In children, bone marrow transplantation is used as a definite treatment method in many diseases including hemoglobinopaties, immune deficiencies, bone marrow failure and congenital metabolic diseases in addition to hematological malignancies. In addition to the underlying disease, the most important factors which have an impact on prognosis include infections which develop during the process of transplantation and graft-versus-host disease. In this article, it was aimed to give brief information on stem cell sources, preparation therapies, HSCT indications and post-transplantation complications in children. (Türk Ped Arş 2014; 49: 91-8)

Key words: Childhood, hematopoetic stem cell transplantation, cord blood transplantation

Bone marrow transplantation has an important place in treatment of many diseases occuring in the childhood including hematologic malignancy, immune deficiency, hemoglobinopathy, bone marrow failures and congenital metabolism disorders. It is a part of the treatment protocols in some of these conditions or the only treatment option in some others. The first allogeneic stem cell transplantation was performed in 1957 by Thomas et al. (1). Definition of human leukocyte antigens (HLA) enabled tissue compatibility between the patient and the donor and this development constituted the most important step in the succes of transplantation. The first successful stem cell transplantations in the history started in 1968 with subjects diagnosed with severe combined immune deficiency (SCID) and Wiskott-Aldrich (2, 3). The first successful non-relative transplantation was performed in 1973 in a 5-year old subject with a diagnosis of SCID. The chance of finding non-relative donors increased as a result of development of bone marrow and cord blood banking and the chance of finding compatible donors increased with use of cord bloods. Currently, more than 20 000 transplantations are being performed and the total number of transplantations has exceeded 200 000 (4). Recently, the term 'hematopoetic stem cell transplantation (HSCT)' has become preferable instead of 'bone marrow transplantation' with introduction of other stem cell sources including peripheral blood stem cell (PBSC) and cord blood. In the last decade, the number of usage of bone marrow has remained unchanged, while the number of usage of PBSC and cord blood has increased (5).

Stem cell sources

Bone marrow

The stem cell source which is considered as a classical source for hematopoetic stem cell transplantation is bone marrow. Bone marrow is collected from the posterior iliac crest under general anesthesia. The determinant for adequacy of the collected bone marrow is the number of nucleated cells. The recommended number of nucleated cells for a successful "engraftment" is 2-4x108 per body weight of recipient. Administration of granulocyte colony stimulating factor to increase the amount of stem cells in the bone marrow has been reported in adult donors, but there are very limited number of data related with pediatric donors (6).

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Peripheral blood stem cell

The stem cell source preferred by many centers in autologous transplantation is peripheral stem cell. In recent years, peripheral blood stem cell (PBSC) has been used with an increasing frequency in relative and non-relative adult donor transplantations. Similarly, it has been used with an increasing rate in pediatric donors (7-9). Although there are drawbacks related especially with pediatric donors, there are publications in the literature reporting that the method is safe and the desired cell number can be achieved easily (10-13). The major advantage related with usage of peripheral blood stem cells is the fact that the expected neutrophil and platelet engraftment times are shorter which results in decreased rates of infectious problems, shorter hospitalization times and decreased need for transfusions. All of these factors affect the cost of transplantation directly. However, the procedure of collection itself (especially problems related with providing an appropriate venous access), potential short-term and long-term side effects of the drugs used in mobilization and increased risk of graft versus host disease (GVHD) are the main points which should be considered in the decision of usage (14).

Cord blood

Cord blood was used as a stem cell source about 30 years ago for the first time and it has been used as an alternative stem cell source with an increasing rate since that time. Its major advantage is easy accessability and low risk of viral contamination and GVHD. In addition, it can be used immediately without a need for donor preparation and its use with 1-2 HLA incompatibilities especially in subjects with rare tissue groups is possible (15). The most limiting factor for its use is the limited number of cells. The lowest acceptable cell numbers are $2.5x10^7$/kg and $1.7x10^5$/kg for nucleated cells and CD34+ cells, respectively (15). Low cell numbers may cause to graft failure. When compatibility of human leukocyte antigens is also considered, the recommended cell dose is $>3.0x10^7$/kg for 6/6 HLA compatible cord blood, $>4.0x10^7$/kg for 5/6 HLA compatible cord blood and $>5.0x10^7$/kg for 4/6 HLA compatible cord blood (16). In recent years, applications directed to increase the low cell number which is the major problem in cord blood transplantation have been tried including ex-vivo expansion, transplantation with double cord blood and peripheral blood stem cell infusion from the same donor simultaneously with cord blood transplantation (17-22). In cord blood, compatibility for HLA-A and HLA-B at the antigen level (low or moderate resolution) and compatibility for HLA-DRB1 at the allele level are considered standard compatibility.

Preparation regimes

The aim of preparation regime in hematopoetic stem cell transplantation is preparation of the patient for the transplantation and it has three different components: "providing space in the bone marrow", "immunosupression" and "elimination of the disease". Providing space in the bone marrow is necessary for the donor's stem cells to reach the "niche" and for "engraftment". Rejection of the graft by the recipient's immune cells can be prevented by immunosupression. Since long-term prognosis is related with disease control in malignancies, the main objective of preparation regime in this group is elimination of the disease. The fact that the side effects of preparation regime are generally tolerated better in children compared to adults allows higher doses. On the other hand, regimes in which total body irradiation (TBI) is performed may lead to late complications including growth retardation, pubertal failure or delayed puberty which are more important especially for the childhood age group. In many studies comparing total body irradiation-based regimes with protocols containing only chemotherapy, no difference could be demonstrated in terms of prognosis. Therefore, it is recommended that TBI-based regimes should be avoided in young children and not be applied at all in children below the age of two years. The most commonly used regimes in children are the regimes in which cyclophosphamide and busulphan are used together (23). Different chemotherapeutic agents may also be added according to the underlying disease especially in congenital genetic diseases.

Decreased intensity regimes have come to the forefront in order to decrease the side effects of preparation regimes. However, experience in children in this area is more limited. In decreased intensity protocols, the most commonly used agent is fludarabine and different agents are added according to the protocol.

Indications for HSCT in children

Indications for HSCT recommended by the EBMT (European Blood and Marrow Transplantation) group based on current clinical practices in Europe are shown in Table 1 (24).

Acute myeloblastic leukemia

Since better results are obtained with multiple agent chemotherapy protocols in pediatric acute myeloid leukemia (AML) patients who are in the low risk group, transplantation is not recommended as the first-line therapy (25). Allogeneic transplantation should be absolutely performed in high-risk AML patients who have a human leucocyte antigen compatible intra-familial donor (24-26). If there is no human leucocyte antigen compatible intra-familial donor, autologous transplantation can be performed (27). However, transplantation from a non-relative donor should be considered in infants with AML or M0, M6, M7 subtypes, if there is no HLA compatible intra-familial donor. Similarly, allogeneic transplantation is indicated in cases of relapse (from intra-familial donor, if present and from non-relative donor, if there is no intra-familial donor) (24).

Acute lymphoblastic leukemia

In acute lymphoblastic leukemia, HSCT is limited to very high risk patients by many centers in the first complete re-

Table 1. HSCT indications recommended in children (EBMT 2009) (24)

		Allogenic			
Disease	Disease status	Sibling donor	Compatible non-relative donor	>1 Ag incompatible relative and non-relative donor	Autologous
AML	CR1 (low risk)	GNR	GNR	GNR	GNR
	CR1 (high risk)	S	CO	GNR	S
	CR1 (very high risk)	S	S	CO	CO
	CR2	S	S	S	S
	>CR2	CO	D	D	GNR
ALL	CR1 (low risk)	GNR	GNR	GNR	GNR
	CR1 (high risk)	S	CO	CO	GNR
	CR2	S	S	CO	CO
	>CR2	S	S	CO	CO
KML	Chronic phase	S	S	D	GNR
	Advanced phase	S	S	D	GNR
NHL	CR1 (low risk)	GNR	GNR	GNR	GNR
	CR1 (high risk)	CO	CO	GNR	CO
	CR2	S	S	CO	CO
Hodgkin's disease	CR1	GNR	GNR	GNR	GNR
	First relapse, CR2	CO	D	GNR	S
MDS		S	S	D	GNR
Primary immune deficiencies		S	S	S	NA
Thalassemia		S	CO	GNR	NA
Sickle cell anemia (high risk)		S	CO	GNR	NA
Aplastic anemia		S	S	CO	NA
Fanconi anemia		S	S	CO	NA
Blackfan-Diamond anemia		S	CO	GNR	NA
CGD		S	S	CO	NA
Kostman syndrome		S	S	GNR	NA
MPS-1H Hurler		S	S	CO	NA
MPS-1H Hurler Scheie (severe)		GNR	GNR	GNR	NA
MPS-VI Maroteaux-Lamy		CO	CO	CO	NA
Osteopetrosis		S	S	S	NA
Ewing sarcoma (high risk or >CR1)		D	GNR	GNR	S
Soft tissue sarcoma (high risk or >CR1)		D	D	GNR	CO
Neuroblastoma (high risk)		CO	GNR	GNR	S
Neuroblastoma >CR1		CO	D	D	S
Wilms tumor >CR1		GNR	GNR	GNR	CO
Osteogenetic sarcoma		GNR	GNR	GNR	D
Brain tumors		GNR	GNR	GNR	CO

GNR: generally not recommended; S: Standard; CO: depending on the decision of the transplantation center; D: experimental; CR: complete remission; MDS: myelodisplastic syndrome; CGD: chronic granulomatous disease; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; KML: chronic myeloid leukemia; NHL: Non-Hodgkin lymphoma

mission. If high risk patients have HLA compatible sibling donor, allogeneic transplantation should be performed (24). In patients who develop early relapse, transplantation from a HLA compatible relative or non-relative donor, if there is no HLA compatible relative is indicated. If a HLA compatible donor can not be found, non-relative cord blood or haploidentic intra-familial donor can be used (28-30). Experience with autologous transplantation in acute lymphoblastic leukemia is very limited and it can be considered in children with late bone marrow relapse or extramedullar relapse (Table 1) (24, 31).

Chronic myeloid leukemia

The incidence of childhood chronic myeloid leukemia is below 1/100 000 and the only treatment method which has been proved to be curative is stem cell transplantation. Transplantation especiallly in the early phase of the disease is recomended in patients who have intra-familial or non-relative donors who show full HLA compatibility (32). However, the success achieved by tyrosine kinase inhibitors in this patient group with a long lifespan expectancy caused to discussions related with necessity of transplantation and timing.

Lymphoma

In pediatric lymphoma patients, it is possible to ensure long-term disease-free survival with autologous HSCT in cases of unresponsiveness to chemotherapy or radiotherapy or in cases of recurrent disease (24). The role of allogeneic transplantation is not clear yet. However, it has been observed that event-free survival is better in lymphoblastic lymphoma subtype with allogeneic transplantation (4% vs. 40%). Although acceptable results are obtained with allogeneic transplantation in cases of relapse and in refractory patients in Hodgkin lymphoma, relapse is still the most important cause of treatment failure (33).

Myelodysplastic syndrome

The treatment method recommeded by many centers for myelodysplastic syndrome (MDS) and secondary AML is allogeneic HSCT from a sibling or non-relative donor who has full HLA compatibility (24). Juvenile myelomonocytic leukemia is a myelodysplastic and myeloproliferative disease with a high mortality rate which is observed rarely in the early childhood. The survival rate is below 10%, if allogeneic transplantation is not performed.

Hemophagocytic lymphohistiocytosis

The only curative treatment method in patients with familial hemophagocytic lymphohistiocytosis (HLH) is allogeneic HSCT. Transplantation can also be curative in refractory or recurring cases (34, 35). These patients may present with a picture similar to X-linked lymphoproliferative disease, Griscelli and Chediak-Higashi and response to HSCT is obtained (36). Haploidentic transplantation has also come to the forefront in this patient group because of the patients in whom transplantation from relative or non-relative donors with full compatibility was performed and who showed a good prognosis (37, 38).

Primary immune deficiencies

Currently, the only accepted curative treatment method is allogeneic HSCT in the majority of immune deficiencies. This group includes severe combined immune deficiency, various T cell deficiencies, Wiskott-Aldrich syndrome, leukocyte adhesion defect, chronic granulomatous disease, Chediak-Higashi syndrome, Griscelli syndrome, familial lymphohistiocytosis and X-linked lymphoproliferative disease. In this patient group, transplantation from a non-relative donor is also indicated, if there is no HLA compatible intra-familial donor (24).

Severe combined immune deficiency is one of the pediatric emergency cases in which immediate transplantation is required following diagnosis. Transplantation can be performed without preparation regime or GVHD prophylaxis treatment, if a HLA compatible sibling is present. If there is no HLA compatible sibling donor, transplantation from alternative donors should be considered, but preparation regime is recommended in such cases (39). In the period after transplantation, T cell functions improve rapidly. While B cell functions generally improve in B (+) SCID patients, improvement is not observed in 40% of B (-) patients. Presence of lung infection, B (-) type and delayed diagnosis are the main factors which affect the prognosis negatively (24).

Acquired severe aplastic anemia

Transplantation is the first treatment option in patients with severe aplastic anemia who have a HLA compatible sibling donor. If there is no HLA compatible intra-familial donor, immunosupressive treatment including ATG and cyclosporine should be tried primarily. In patients who are not responsive to this treatment, transplantation from non-relative donors or from cord blood is indicated (24, 40, 41).

Hereditary bone marrow failure syndromes

Fanconi anemia: Fanconi anemia (FA) is a rare genetic disease characterized with progressive bone marrow failure and predisposition to malignancy (especially AML) accompanied by various physical anomalies. The only way to correct hematological disorder in patients with Fanconi anemia is HSCT and transplantation from a HLA compatible sibling, relative donor or non-relative donor can be performed (42). The major characteristic of Fanconi anemia is hyperensitivity of the cells to cross-linking agents including diepoxybutan or mitomycin C and chromosomal imbalance. The clinical significance of the disease in terms of transplantation is the fact that toxicity with classical preparation regimes is very high. In the light of this information, use of fludarabine-based low-toxicity regimes and avoiding irradiation have recently come to the forefront (43-45). Additionally, GVHD-related tissue damage has a more severe prognosis because of defect in cell repair mechanisms (42). In patients who have no HLA compatible donor, trans-

plantation with non-relative cord blood can be considered. In the period following transplantation, the patients should be closely monitored in terms of various organ dysfunctions and increased malignancy risk (especially squamous cell carcinoma and hematological malignancies) (46, 47).

Diamond Blackfan anemia: This is a hereditary type of anemia characterized with decreased erythroid procursors or absence of erythroid procursors in the bone marrow. Allogeneic HSCT is indicated in patients who have HLA compatible sibling donors and who are not responsive to steroid. While the 5-year survival has been reported to be 87.5% for transplantations performed from HLA compatible sibling donors, the outcomes are not satisfactory for transplantations performed from alternative donors (48).

Amegakaryocytic thrombocytopenia: This is an autosomal recessive genetic disease which becomes symptomatic in the days or weeks following delivery. The only curative treatment method is allogeneic HSCT (49, 50).

Congenital neutropenia: This disease is characterized with severe neutropenia and severe bacterial infections starting from the early period of childhood. HSCT is indicated even if there is no HLA compatible intra-familial donor in patients who are not responsive to granulocyte colony stimulating factor or who develop MDS/AML (51, 52).

Hemoglobinopathies

β-Thalassemia and sickle cell anemia are the most common single gene diseases worldwide. Although marked improvement is achieved in clinical findings and quality of life with regular transfusions and chelation and supportive therapies including hydroxyurea for sickle cell anemia, it is not possible to eliminate the disease and prevent treatment-related complications with these approaches. Currently, it is accepted that HSCT is the only curative treatment method also for this patient group. In series from many different countries, a disease-free survival of 75-80% has been reported with HSCT in beta thalassemia (53-56). Prognosis is much better especially in patients with young age who are in the low risk group. Therefore, HSCT is recommended to be performed in the early childhood before iron load and disease-related complications develop. In recent years, positive outcomes have been reported for transplantations from relative donors without full HLA compatibility or HLA compatible non-relative donors. However, this is not being performed regularly yet. GVHD rates have recently been reported to be low in transplantations performed with cord blood in patients with β thallasemia and/or sickle cell disease. However, graft failure and recurrence of the disease are still important problems for cord blood transplantation (57).

Metabolic diseases

Metabolic diseases with an indication of transplantation are generally in the group of lysosomal storage disease. It is based on transfer of the deficient enzyme from donor cells to the reticuloendothelial system and solid organs (24). The diseases for which we have the greatest experience include adrenoleukodystrophia, type 1 mucopolysaccaridosis (Hurler syndrome) and osteopetrosis.

Solid tumors

The European Group for Blood and Marrow Transplantation data have shown that transplantation prolongs the course in pediatric cases of neuroblastoma and Ewing tumor (24, 58, 59). In other solid tumors, the patients may benefit from autologous transplantation in presence of the following special conditions (24):

Germ cell tumors: in presence of relapse or progressive disease,

Soft tissue sarcoma: Stage 4 or following relapse without a chance for resection,

Wilm's tumor: in presence of high risk histology or relapse,

Brain tumors: Medulloblastoma with response to chemotherapy or high grade gliomas.

Transplantation related complications

High dose radiotherapy and/or chemotherapy used in preparation regimes may affect all organs of the recipient and lead to early or late secondary effects with varying severity. It is known that development of complications may be related with individual predisposition, immunosupressive therapies, toxicities related with pre-transplantation therapies and presence of other accompanying factors during transplantation (60).

Graft versus host disease

Graft versus host disease is one of the most important complications of allogeneic complications of transplantation. Although the risk is lower in pediatric patients compared to adults, its frequency has increased especially with use of alternative donors.

Graft versus host disease occurs as a result of recognition of the antigens of the recipient by T cells as foreign antigens. It may be classified in two different groups as acute GVHD (aGVHD) and chronic GVHD (cGVHD). In the differentiation of acute and chronic GVHD, the initiation time is used generally and cases which develop before the 100^{th} day are named as acute and cases which develop after the 100^{th} day are named as chronic GVHD. Occasional overlaps between the two groups suggest that these definitions are not determinative enough. The clinical outcomes of these two groups are different and different treatment methods are required based on immunological differences. The most important risk factor is incompatibility between the recipient and donor. As the rate of incompatibility increases, the risk of GVHD increases. It has been reported that the risk of GVHD increases in patients in whom peripheral blood is used as the source of stem cell and the risk is lower when cord blood is used. The frequency

of grade ¾ aGVHD has been reported to be as high as 30-50% in non-relative transplantations (61, 62). A marked improvement in GVHD rates has been obtained as a result of development of high resolution method and determination of 10 HLA loci at the allele level with this method in non-relative donors (63). Other factors which are thought to carry a risk in terms of GVHD include advanced age of the recipient and donor, gender incompatibility (especially when the recipient is male and the donor is a multiparous female), presence of malign disease and use of intensive preparations regimes.

Three phases have been described in the pathophysiology of acute GVHD: tissue damage caused by the preparation regimes, activation and proliferation of the donor's T cells and occurence of damage in the recipient (64). Tissue damage caused by the preparation regimes leads to uncontrolled release of cytokines including interferon-γ (IFNγ), interleukin-1 (IL-1) and tumor necrosis factor-α (TNFα). Release of these cytokines increases MHC expression in various tissues of the recipient and exacerbates graft versus host activity of the donor's T cells. The small intestines and liver are especially sensitive to organ damage caused by myeloablative regimes. Therefore, it has been proposed that the risk of GVHD is higher in patients in whom intensive diarrhea is observed in relation with the preparation regime (65). In the second phase, the antigen presenting cells of the recipient and donor stimulate the T cells derived from the donor together with the inflammatory cytokines and cause them to increase in number and transform into effector cells. Induction of T cell proliferation initiates the third phase and the inflammatory cytokines released from the T cells including IL-2, IFNγ and TNF lead to direct or indirect tissue damage in the recipient. In addition to cytotoxic soluble vehicles, cellular cytotoxicity including perforin-granzyme-B-mediated cytolysis and Fas-Fas ligand-mediated apoptosis have important roles in the pathogenesis (64, 65). This three-phase event leads to special clinical pictures in which the skin, intestines and liver are affected at varying degrees and grading can be made according to involvement rates.

Since graft versus host disease generally shows a bad prognosis, prophylactic approaches directed to prevent its development are more important compared to treatment. Cyclosporin A, takrolimus, MMF (Mycophenolate Mofetil), methotrexate and metylprednisolone are used as prophylactic agents.

The mortality rate is markedly low in patients who show early response to low dose steroid treatment. However, patients who do not give early response should be evaluated in terms of other immunosupressive drugs without delay. New drugs, new monoclonal antibodies, complementary therapies and immunomodulator procedures including intensive immunosupression and extracorporal photopheresis may provide remission, but side effects of these therapies and especially infections are important problems which should be solved. Immunotolerance with cellular therapies (mesenchymal stem cells)is possible and appears to be promising.

The pathophysiology of chronic GVHD (cGVHD) has not been elucidated as well as the pathophysiology of the acute form. It is thought that both donor-derived alloreactive T cells similar to AGVHD and autoreactive T cell clones which can not be deleted as a result of thymic damage are involved (66, 67). The main feature of many clinical findings in chronic GVHD (cGVHD) is diffuse collagen deposition and the clinical prognosis generally resembles autoimmune diseases.

Infectious complications

Infectious complications are among the most important causes of transplantation-related morbidity and mortality. Presence of graft versus host disease, delayed immune reconstitution and allogeneic transplantation compared to autologous transplantation are the most important risk factors. The subjects are given antibacterial, antifungal and antiviral prophylactic treatment in addition to a preparation regime (68-72).

Non-infectious complications

Gastrointestinal and hepatic complications
- Mucositis
- Venoocclusive disease (sinusoidal obstruction syndrome)

Pulmonary complications
- Pulmonary edema,
- Bacterial, fungal and viral infections,
- Idiopathic pneumoniae syndrome
- Diffuse alveolar hemorrhagia

Renal complications
- Nephrotoxicity,
- Hemolytic uremic syndrome-Thrombotic microangiopathy
- Hemorrhagic cystitis

Cardiac complications
- Cardiotoxicity,
- Conduction disorders
- Intracardiac thrombosis related with catheter

Late endocrinological complications
- Hypothyroidism,
- Adrenal insufficiency (related with use of steroid),
- Testicular or ovarian insufficiencies,
- Developmental retardation

Secondary cancers

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