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REVIEW ARTICLE

Hematopoetic stem cell transplantation in children

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Abstract:
Hematopoietic stem cell transplantation (HSCT) has been an established as a curative therapy for the various hematologic nonmalignant and malignant diseases in childhood. In addition to conventional indications like hematological malignancies, aplastic anemia and solid tumours, a gerat deal of inborn errors in children can be cured with HSCT. Recent applications and recommendations in terms of stem cell sources, indications, conditioning and post-transplant complications in children like infectious complications, graft versus host disease (GVHD), gastrointestinal and liver complications, pulmonary complications and late endocrine effects are discussed in this review.

Keywords: *hematopoietic stem cell transplantation, children, stem cell source, indications, complications, supportive therapy, late effects*
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Inroduction

Hematopoetic stem cell transplantation has been established as a curative therapy method in various malign and non-malign disorders. The first allogeneic hematopoietic stem cell transplantation (HSCT) was performed by Thomas et al [1] in 1957. After the discovery of the human leukocyte antigens (HLAs) matching between patient and donor became possible leading to increased transplantation success. The first successful bone marrow transplants were done in children with severe combined immunodeficiency (SCID) and Wiskott-Aldrich diseases in 1968 [2,3]. In 1973, the first successful unrelated bone marrow transplantation in children was performed in a 5 year old child with SCID. After that, the number of bone marrow transplants performed worldwide increased substantially. The use of unrelated donors and umbilical cord blood (UCB) grafts has increased the possibilities of finding a suitable donor. Now, almost more than 20.000 transplants are performed yearly with more than modality for many diseases in children, including hematologic malignancies, immundeficiencies, hemoglobinopathies, bone marrow failure syndromes and congenital metabolic disorders.

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Recently, terminologically, "hematopoietic stem cell transplantation" has been preferentially used instead of "bone marrow transplantation" because of additional alternative stem cell sources like peripheral blood stem cells (PBSC) and umbilical cord blood. Although the number of bone marrow (BM) donations has been stable over the past 10 years, donations of PBSCs and umbilical cord blood has been increasing [4,5].

Sources of Stem Cells

Bone Marrow

The classical source of hematopoietic stem cells for HSCT is bone marrow. Bone marrow is typically collected from the posterior iliac crest of the donor under general anesthesia. The adequacy of the collection is determined by the nucleated cell count. Target counts for successful engraftment are typically 2 to 4 $x10^8$ nucleated cells per kilogram of the recipient's body weight [6]. Although there are some reports for adult bone marrow donors receiving G-CSF to enrich stem cells, experience with pediatric donors is limited [7].

Peripheral Blood Stem Cells

Many centers prefer to use of PBSC in the setting of autologous transplantation. Recently, in allogeneic HSCT from sibling or unrelated donors PBSC donation is becoming more prevalent worldwide as an alternative source of hematopoietic stem cells rather than bone marrow derived stem cells in adults. Similarly, PBSC have been increasingly used also in pediatric transplantations [8-10]. Although some hesitations have arised for healty pediatric donors there are some reports that PBSC collection is safe in normal pediatric donors and desired CD34 cell yields are easily achieved [11-14].

The most striking advantages of transplantation with allogeneic PBSC are expectation of more rapid neutrophil and platelet engraftment with possibly lower incidence and severity of infectious complications, a shorter stay in hospital and a lesser need for transfusional support. These are reflecting lower transplantation cost. On the other hand at least three possible problems should be considered in contrast to possible advantages of PBSC while deciding, that are problems related to the collection procedure itself, in particular the venous access; the use of mobilizing drugs and, last but not least, the increased risk of severe GVHD, possibly related with infusing a higher (5-10 times) number of lymphoid cells [15].

Umbilical Cord Blood

Since the first umbilical cord blood (UCB) transplant, performed 20 years ago, UCB has being increasingly used as alternative hematopoietic stem cell source. Easy availability, lower risk of viral contamination and GVHD are the advantages of UCB. In addition, UCB units are almost immediately available for transplant and permissive 1-2 HLA mismatching for patients with uncommon tissue types [16]. The main limitation to use is lower cell count. The current accepted threshold limits for CD34+ and nucleated cells are $1,7x10^5$ cell/recipient body weight and $2,5x10^7$ cells/recipient body weight, respectively [16, 17]. Low cell count may lead to graft failure. Recently, ex-vivo expansion, double units transplantation and co-infusion of peripheral blood stem cells from a third party donor have been suggested to improve the outcome of UCB transplantation [18-23]. On the other hand, Ballen et al [24] reported second myeloid malignancies of donor origin occuring after double umbilical cord blood transplantation, suggesting that a search for donor origin should be performed in all patients with suspected relapse.

Although HLA matching at antigen level (low or intermediate resolution) for HLA-A and -B and allele level matching for HLA-DRB1 continues to be the current standard for CB unit selection, some retrospective analyses have evaluated the impact of undetected allelic disparities in a subset of UCBT recipients [25,26]. However, to determine the real value of allele typing in UCBT, thousands of patients–donors pairs will be needed to reach statistical significance [27]. A higher cell dose in the graft could partially overcome the negative impact of HLA for each level of HLA disparity, but this hypothesis has not been yet been fully demonstrated [27]. Nowadays, many authors spend much effort on future of cord blood for oncology and non oncology uses [28,29].

Conditioning regimens

The aim of conditioning is to prepare the patient for HSCT. It is given to patient with three main objectives; "creation of space", "immunosuppression" and "disease eradication". Creation of space in marrow stroma is necessary for donor stem cells to obtain access to the niches and for engraftment to occur. It is well known that immunosuppression is required to prevent rejection of the graft by host immune cells. However, rejection is also increased in T cell depleted HSCT meaning

that sufficient numbers of T cells are required for engraftment. The role of conditioning regimen in disease eradication is important in patients with malignancies in which long term disease control is the main objective of trasnplantation. Generally, children can tolerate the side effects of conditioning better than older patients that allows applying higher total doses. On the other hand, total body irradiation (TBI) based conditioning regimens may cause growth retardation as well as pubertal failure or retardation as late sequelae in pediatric patients. There are many reports comparing TBI based regimens with those containing only chemotherapy with similar outcomes. Therefore, most of the authors recommended that TBI should be avoided in small children and never be given to children below 2 years old. However, some ALL studies showed better survival with TBI/cyclophosphamide [30]. The most commonly used conditioning regimen in pediatric patients is busulphan combined with cyclophosphamide [31]. Some additional chemotherapeutics or different regimens are used according to underlying disease in patients with inborn errors.

Because of short and long term morbidity and mortality risk of conventional myeloablative conditioning regimens recently milder and less toxic regimens have been developed. Minimum requirements for successful engraftment include sufficient immune supression to promote short-term engraftment of hematopoetic precursors while the donor lymphocytes contained within the graft obtain donor chimerism and satisfactory antitumor effect to maintain post-transplant remission [32]. Reduced intensity conditioning (RIC) is used to replace defective host hematopoesis with normal donor cells or to provide a missing factor or enzyme in the host in patients with non-malignant diseases. In case of malignancy the main goal is to induce an optimal graft-versus-leukemia (GVL) effect by donor alloreactive effector cells while minimizing toxicity [33]. Fludarabine (FLU) is the most commonly used drug in RIC regimens. Seattle protocol, as an example, consists of FLU, low dose TBI and post-transplant Cyclocyporin A and mycophenolate mofetil [34]. Some clinical trials have been published assessing this approach in children with malign or nonmalignant disorders [35-41]. However, multicenter prospective studies with large pediatric population are needed to define the optimal regimens and appropriate candidates for RIC.

HSCT indications in Children

Proposed classification of HSCT indications for children by EBMT according to current clinical practice in Europe is shown in Table 1 [42].

Acute myeloid leukemia

In patients with good risk AML, HSCT is not recommended as frontline therapy because of better outcome with modern multiagent chemotherapy [43]. High risk (HR) AML patients, on the other hand, if HLA identical sibling donors are available, are absolutely candidate for allogeneic HSCT [42-44]. If they don't have matched sibling donor, autologous HSCT can be performed as an alternative [45]. EFS in children with AML who underwent autologous HSCT was reported as 60% by EBMT covering 387 children [46]. However, infant AML, M0, M6, M7 subtypes are indications for unrelated donor HSCT. In relaps AML patients, allogeneic HSCT is indicated either from a matched sibling or an unrelated donor [42].

Acute Lymphoblastic Leukemia

Most of the centers perform limited HSCT in CR1, only in a group of very HR ALL. Some laboratory and clinical features like molecular biological markers, chromosomal abnormalities, poor prednisone response or resistance to initial chemotherapy are established risk factors in children with ALL and used to stratify patients into risk groups. A child with high risk ALL should undergo allogeneic HSCT if HLA matched sibling donor is available [42]. BFM group reported 5-year-disease free survival (DFS) in high risk childhood T cell ALL patients who received HSCT in CR1 and treated with chemotherapy alone as 67% and 42%, respectively [47]. Similarly, Balduzzi et al [48] reported 5-year-DFS in very high risk ALL patients as 57% in MRD HSCT group and 41% in chemotherapy group.

Both HLA matched sibling and unrelated donor HSCT are clearly indicated in patients who experience an early relapse. If a matched donor is not available, unrelated UCB, mismatched unrelated

donors or haploidentical family donors can be indicated [49-51]. Klingebiel et al [52] suggested that higher CD34(+) cell dose and better patient's selection may improve outcomes of children with ALL given a haploidentical HSCT in experienced centers. Autologous HSCT is very limited in children with either a late bone marrow relapse or an extramedullary recurrence (Table 1) [42,53].

Chronic Myeloid Leukemia

The incidence of CML in childhood is less than 1 in 100.000. HSCT is the only proven curative treatment for children with CML so these patients are good candidate for HLA-identical or matched unrelated donor HSCT in the early period of the disease [54]. However, a success of tyrosin kinase inhibitors (TKI) has raised contraversies about indication and timing of HSCT. On the other hand, obligations of a lifelong medication with TKI, treatment failures or TKI refractoriness are the limitations. Recently, it has been reported by EBMT that HSCT might be postponed for patients achieving a hematological response at 3 months, followed by a minor cytogenetic response at 6 months and followed by a complete cytogenic response at 12 months after start of TKI (imatinib) at a dose of 300 mg/m2 [42].

Lymphoma

Children with lymphoma who fail to respond chemotherapy and radiotherapy or with recurrent disease can achieve long term disease free survival after autologous HSCT [42]. However, the role of allogeneic HSCT has not been clarified, yet. Gross et al [55] compared aoutologous and allogeneic HSCT results for refractory or recurrent non-Hodgkin lymphoma in children and adolescents. In this study 5-year-EFS were similar between two groups in diffuse large B-cell lymphoma (50% vs 52%), Burkitt (31% vs 27%), and anaplastic large cell lymphoma (46% vs 35%). However EFS was higher for lymphoblastic lymphoma after allogeneic HSCT (40% vs 4 %). Although reasonable results with allogeneic HSCT for relapsed or refractory Hodgkin lymphoma have been reported, relaps remains the major cause of treatment failure [56].

Myelodysplastic Syndrome

The most center suggested that allogeneic HSCT from a sibling or matched unrelated donor is the treatment of choice for children with MDS or secondary AML (42). Juvenil myelomonocytic leukemia (JMML) is a rare, fatal mixed myelodysplastic and myeloproliferative disorder in early chilhood. Probability of survival without allogeneic HSCT is less than 10% and resuls of sibling or matched unrelated donor are similar. However, high relaps and mortality rate is of great concern [57-59].

Hemophagocytic Lymphohistiocytosis (HLH)

Allogeneic HSCT is the main curative treatment in familial HLH. Allogeneic HSCT aims to replace immun system inducing a definitive cure in patients with familial, persistant and recurrent disease [59, 60]. Patients with X-linked lymphoproliferative disease, Griscelli and Chediak-Higashi may also present with a similar clinical picture and respond to HSCT [59]. Some reports showing well going HLH patients transplanted from MRD or MUD suggest that haploidentical donors are also acceptable in this group of patients [60, 61]. Because of the possible risk of a sibling carrying the disease if a genetic marker (such as for PRF, UNC13D, or STX11) is not available, NK-cell activity can be considered as a helper marker of immune dysfunction, although healthy siblings may also have persistently decreased NK-cell activity [62].

Primary Immunodeficiencies (PID)

Allogeneic HSCT is the only curative treatment of immundeficiencies including severe combined immundeficiencies (SCID), several T-cell immundeficiencies, Wiskott-Aldrich syndrome, leukocyte adhesion deficiency, chronic granulomatous diseases, Chediak-Higashi syndrome, Griscelli's syndrome, familial lymphohistiocytosis and X-linked lymphoproliferative syndrome. Allogeneic HSCT is indicated in severe PID from both HLA-identical and alternative donors [42].

SCID is an one of the pediatric emergency that needs to be grafted as soon as possible once diagnosis is confirmed. If HLA genotypically identical donor is available HSCT can be performed without any conditioning or GVHD prophylaxis. In the absence of a HLA genoidentical sibling, HSCT can be performed with a phenotypically identical family donor, a phenoidentical cord blood, a matched

unrelated donor or a haploidentical family donor (parents). The use of conditioning regimen is recommended in these cases [63]. T-cell functions develop rapidly in post-transplant period. In patients with B (+) SCID B cell functions nearly always improve however it is absent in 40% of those with a B(-) form . Presence of lung infection, B (-) type and late diagnosis are the main factors for poor prognosis [42].

Acquired Severe Aplastic Anemia (SAA)

Acquired SAA is a clear indication for allogeneic HSCT in children with HLA-identical sibling. If there is no HLA matched family donor, immunosuppressive therapy with ATG and cyclosporine A is indicated. For children who have no response to a course of immonusupressive therapy, unrelated donor or cord blood transplantation should be considered [42,64,65]. EBMT Working Party on Severe Aplastic Anemia reported significant improvement in survival in patients transplanted after 1998 as compared to earlier cases and explained this improvement with high-resolution HLA typing technology and possibly, improved infection control [66]. Maury et al [67] also reported improved outcome in the era of high-resolution HLA matching between donor and recipient. Recently, Hagasaki et al [68] compared matched-sibling donor BMT and unrelated donor BMT in children and adolescent with acquired SAA and reported 10 year disease free survival as 96.7% and 84.7%, respectively.

Hereditary Bone Marrow Failure Syndromes

Fanconi anemia (FA) is a rare genetic disorder characterized by variable number of somatic abnormalities, progressive bone marrow failure and predisposition to malignancy particularly to the development of acute myeloid leukemia. HSCT from healthy donors is the only treatment modality for the correction of hematological abnormalities in FA patients. Allogeneic HSCT should be performed if they have a normal HLA identical sibling, matched family or unrelated donor [69]. FA cells are hypersensitive to DNA cross-linking agents such as diepoxybutane (DEB) or mitomycin C, which results in chromosomal instability and cell death. At the clinical level this has translated into severe toxicity when conventional conditioning regimens are used in preparation of FA patients for HSCT. In the light of this issue, recently fludarabine based low toxicity conditioning regimens excluding irradiation have been proposed [70-72]. In addition, GVHD induces severe tissue damage with delayed or absent tissue repair [69]. Unrelated cord blood transplantation results are acceptable in patients who do not have a HLA identical sibling donor. Eurocord analyzed the results of unrelated CB transplantations in 93 FA patients [73] and identified favorable factors as the use of FLU, high number of cells and negative recipient CMV serology. In post-transplant period, FA patients should be followed closely for various organ dysfunctions and increased risk of developing malignancies especially for squamous cell carcinoma and hematological malignancies [74,75].

Diamond Blackfan Anemia (DBA) is an inherited anemia with absent or decreased erythroid precursors in the bone marrow. Allogeneic HSCT is a clear indication in steroid resistant patients if HLA-identical sibling donor is available. The 5-year-survival in HSCT from HLA-identical sibling was reported as 87.5 % by DBA registry. However, results are poor with alternative donors [76].

Congenital Amegakaryocytic Thrombocytopenia (CAT) is an autosomal recessive disorder in which affected infants are identified within days or weeks of birth. Allogeneic HSCT is the only chance of cure in CAT [77,78].

Kostmann Syndrome is an autosomal recessive inherited disorder with severe neutropenia and early onset of severe bacterial infections. Allogeneic HSCT is the treatment of choice in patients refractory to G-CSF or with MDS/AML even there is no HLA identical family donor [79,80].

Hemoglobinopathies

β-Thalassemia and sickle cell disease are the most common genetic diseases worldwide. Although supportive therapies such as regular transfusion and chelation for β-thalasemia and hydroxyurea (HU) for sickle cell disease have significantly improved clinical manifestations and the quality of life, they cannot eliminate the diseases and therapy-related complications. Today, HSCT is the only curative treatment for patients with hemoglobinopathies. A lot of studies from different countries reported that

HSCT is a chance for beta thalassemia patients with 75-80% thalassemia free survival rates [81-84]. Results are better in lower risk group and younger patients. That's why HSCT should be performed in early childhood before iron overload and disease related complications take place. Although successful results have been reported; the use of mismatched related or matched unrelated donors is associated with a higher risk for graft rejection, TRM and GVHD in beta thalassemia [85,86] and it has not been accepted yet as standard application in EBMT guide [42]. Recently, cord blood transplantation (CBT) in patients with either β-thalasemia and/or sickle cell disease has been reported with lower GVHD. However, graft failure and recurrence of disease seem the major problems for CBT in hemoglobinopathies [87].

Better supportive treatments, the use of pneumococcal vaccine or hydroxyurea treatment have improved both the quality and the duration of life for sickle cell patients. So, HSCT has been offered only to a subset of patients with severe form and life-threatening risk.

Metabolic diseases

Most of the disorders in this group for which HSCT is indicated are lysosomal storage diseases and rely on transfer of enzyme from donor-derived blood cells into the reticulo-endotelial system and solid organs [42]. Allogeneic HSCT is recommended routinely children with adrenoleukodystrophy (ALD), Type I Mucopolysaccharidoses (Hurler's syndrome) and osteopetrosis.

Solid tumors

EBMT data results have shown significantly better survival in patients with neuroblastoma or Ewing's tumor [42,88,89]. Prospective and randomized studies have indicated a clear advantage in these patients. Patients with other solid tumors may get benefit from autologous HSCT following high-dose chemotherapy in the following situations [42]:

Germ cell tumors: After a relapse or with progressive disease,

Soft tissue sarcoma: Stage IV or after a non-respectable relapse,

Wilm's tumor: High risk histology or relapse,

Brain tumors: Children with medulloblastoma and high grade gliomas responsive to chemotherapy to avoid or postpone radiotherapy.

Generally, allogeneic HSCT is not recommended in children with solid tumors due to increased regimen related mortality.

Transplant Related Complications

The high dose of radiotherapy and/or chemotherapy included in conditioning regimens affects all organs and tissues of the recipient, leading to early and late secondary effects of variable intensity.

These complications are supposed to related with individual predisposition to developing morbidities, immunosuppressive therapies, pre-transplant treatment related toxicity and existence of comorbid factors [90]. Although the main aim of the HSCT procedure is to cure the underlying disease, a careful assessment to identify, treat and hopefully prevent complications is mandotary for a success of transplantation, especially in the growing child.

Infectious complications:

Infectious complications constitute the major cause of morbidity and mortality in patients having HSCT. The risk of infection is higher in patients having allogeneic transplantation compared to autologous, in patients with GVHD and also with delayed immune reconstitution [91-93]. The use of steroids has been shown to be the most significant variable associating with infectious episodes [94]. After allogeneic HSCT following myeloablative conditioning, depending on the type of immune deficiency as a consequence of gradual immune reconstitution, the sequence of infections can be divided into three periods:

1. Pre-engraftment risk period begins with the onset of conditioning regimen and continues until neutrophil recovery. The cytotoxic agents used as conditioning damage dividing cell populations, particularly bone marrow progenitor cells leading to severe and prolonged neutropenia and also mucosal epithelial cells resulting in defects in mucosal and cutaneous barriers. These abnormalities lead to bacterial and fungal blood stream infections. The

Table 1. Proposed classification of transplant procedures for children (EBMT 2009) (42)

Disease	Disease status	Allo			Auto
		Sibling Donor	Well-matched unrelated	mm unrelated > 1 Ag mm related	
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
CML	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 disease	CR1	GNR	GNR	GNR	GNR
	First relaps, CR2	CO	D	GNR	S
MDS		S	S	D	GNR
Primary immundeficiencies		S	S	S	NA
Thalassemia		S	CO	GNR	NA
Sickle cell disease (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's disease		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
Osteogenic sarcoma		GNR	GNR	GNR	D
Brain tumors		GNR	GNR	GNR	CO

most prevalent pathogens causing infection are streptococci, Gram-negative bacteria, Candida species and, if the neutropenia persists, Aspergillus species. Neutrophil recovery usually marks the end of the bacterial risk for most autologous transplants but not for allogeneic ones.

2. Post-engraftment risk period begins with neutrophil recovery and continues until B and T lymphocyte recovery is apparent that is usually around day 100 and characterized by profound cellular and humoral immune deficiency. It is the period that the cytomegalovirus (CMV) infection has the highest incidence occurring as

either a primary infection in seronegative patients or by reactivation in seropositive patients. The occurrence and severity of GVHD are the main risk factors for infections. Aspergillus infections can also be seen in this period and patients with ongoing GVHD and/or receiving steroids are at higher risk.

3. Late post-transplantation risk period begins at approximately day 100 and ends by the end of discontinuation of immunosuppressive treatment. Encapsulated bacteria commonly S. pneumonia are the major pathogens due to functional hyposplenism. Aspergillus, pneumocystitis jiroveci, several viruses, mainly varicella-zoster virus or respiratory viruses like respiratosy syncytial virus or parainfluenza virus, may lead to severe infections during this period.

Each period of transplantation should be associated with preventive strategies that can be classified as general infection control measures, vaccinations and pharmacological approaches.

Antibacterial prophylaxis

The efficacy of antibacterial prophylaxis with use of cotrimoxazole or quinolones is documented in neutropenic cancer patients or after autologous HSCT but not after allogeneic HSCT, and no study is available for children [95,96]. The only double-blind placebo controlled randomized clinical trial in pediatric population was done with the use of amoxicicillin-clavulanate and did not include HSCT recipients [97]. Owing to lack of data , there are currently no antimicrobial prophylactic regimens that can be recommended for children [98]. However the use of fluoroquinolones is considered safe [99]. Local epidemiological data should be carefully considered before applying fluoroquinolone prophylaxis and once applied monitorization of quinolone resistance is essential. The addition of an anti-Gram positive agent was shown to lack benefit for prophylaxis and their use with this indication was supposed to promote the emergence of resistant organisms [100]. Prophylaxis is usually started at the time of stem cell infusion and should not be continued after neutrophil recovery [98]. The only exception to this strategy may be represented by the prevention of bacteremia due to *S. pneumoniae* by means of long-term prophylaxis in the presence of functional asplenia or severe chronic GVHD [101].

Antifungal prophylaxis

The risk for invasive candidiasis is significantly higher during the preengraftment period because of neutropenia, severe mucositis and the presence of a central venous catheter and continues to be a risk during the post-engraftment period depending on the presence of a central venous catheter and severe gastrointestinal GVHD [102]. In any case antifungal prophylaxis is recommended to be given up to +75 day after allogeneic HCST or during immunosuppressive treatment in case of GVHD [103]. Flucanazole is the drug of choice but may result in the selection of azole resistant candida species [103-105]. Itraconazole or micafungin have been documented to be effective as prophylaxis [106-108]. However the use of itracanazole oral solution is limited with poor tolerability, toxicities and many drug interactions and micafungin has not been studied in pediatric group with this indication.

Invasive mold infections have a trimodal incidence distribution among allo-HSCT recipients. Patients with prolonged neutropenia in preengraftment period and the ones with severe cell mediated immunodeficiency caused by GVHD and its treatment in later period either in phase 2 or 3 are at high risk for mold infections and should be considered for prophylaxis with mold-active drugs during period of risk. Fluconazole has no activity against molds [109] and if antimold activity is warranted in antifungal propyhlaxis, voriconazole and posaconazole are options [110,111]. However data regarding dose and schedule of administration of posaconazole are limited in children. Trials assessing the efficacy of itraconazole have shown efficacy in preventing mold infections but poor tolerance and the toxicity are main limiting factors to use [107, 112]. Micafungin has been shown to be affective in preventing invasive fungal infections during neutropenia but the incidence of invasive aspergillus is low during the preengraftment period, i.e. antimold efficacy could only show activity rather then efficacy [113]. Caspofungin, another echinocandin although has been shown to have efficacy, breakthrough mold infections have been reported during prophylactic usage [114]. Patients with earlier invasive aspergillosis should receive secondary prophylaxis with a mold-active drug and voriconazole has been shown to have benefit for this indication [115].

Antiviral prophylaxis

A prophylaxis strategy against early CMV replication for allo-HSCT recipients involves administration of prophylaxis to all allogeneic recipients at risk throughout the period from engraftment to 100 days after transplant [116]. High dose acyclovir, ganciclovir, valacyclovir have shown to have efficacy in reducing the risk for CMV infection after HSCT [117,119]. The survival advantage of prophylactic ganciclovir usage was not demonstrated and was potentially linked to greater risk of fungal or bacterial infections possibly related with ganciclovir induced neutropenia [120]. The general approach of prevention of CMV disease is treatment of all at-risk patients as preemptive therapy that should be given for a minimum of 2 weeks [121]. The diagnostic tests to determine the need for preemptive treatment include the detection of CMV

pp65 Ag in leucocytes, detection of CMV DNA or RNA. If CMV is still detected after 2 weeks of thearpy, maintenance therapy is recommended until CMV is undetectable or it can be continued up to day 100 [121,122] Ganciclovir is the drug of choice although foscarnet that is currently more commonly used as a second-line drug, is as effective as ganciclovir [(122]. Oral valganciclovir , a prodrug of ganciclovir, although has been increasingly used in preemptive therapy having comparable results with iv ganciclovir or valganciclovir, no data are available in children [123]. Prophylaxis for herpes simplex virus with acyclovir is recommended in seropositive allogeneic recipients from day -1 to day +30. However, VZV seropositive allogeneic or autologous HSCT recipients should receive long- term acyclovir prophylaxis during the first year that may be continued beyond 1 year in patients with chronic GVHD or requiring systemic immunosuppression. Although valacyclovir has been shown to be equally effective and safe in adult HSCT recipients [118,124,125], there are limited date regarding safety and efficacy in children and no recommendations for the pediatric population can be made.

Graft versus host disease

Graft versus host disease (GVHD) is the major complication of allogeneic HSCT. Children are at less risk for GVHD compared to adults but the risk is still significant especially with alternative donor sources. In a large registry-based study of allogeneic matched sibling bone marrow transplants including 630 children with leukemia, the incidence of grade II-IV and grade III-IV aGVHD were reported as 28 and 11 %, respectively [126]. GVHD is a consequence of donor T cells recognizing host-recipient antigens as foreign. It is divided into two broad categories: acute GVHD (aGVHD) and chronic GVHD (cGVHD). The usual distinction between acute and chronic GVHD is mainly based on the time of onset and aGVHD is defined as signs and syptoms developing before day 100 after transplantation, whereas cGVHD begins after day 100. Obviously, some overlap between acute and chronic GVHD exists and this usual distinction is now seen as somewhat arbitrary. The clinical consequences of each are unique and require different strategies to manage as in relation with immunological differences between two.

The risk factors for GVHD are well defined while most of the data come from adult studies. The most important factor is HLA disparity meaning that greater the degree of HLA mismatch, the higher the likelihood of developing GVHD. For unrelated transplantation, up to late 1990s, the approach was to match at HLA A and B at the antigen level and at HLA-DR B1 at the allele level leading to an incidence of aGVHD (grade III/IV) in 30-50% range in children with unmanipulated unrelated bone marrow [127,128]. Prospective high resolution matching of unrelated donor at 10 alleles was documented to lead remarkable decrease in the incidence of grade III/IV aGVHD [129]. In respect to graft type, there is a suggestion from meta-analysis that acute GVHD is slightly increased (relative risk 1.16, $p=0.006$) and chronic GVHD is increased (relative risk 1.53, $p<0.001$) in PBSC recipients compared to bone marrow [130] although no randomized study has been published yet. In a large-retrospective registry study of pediatric leukemia patients published by Eapen et al [126], the incidence of grade II-IV and III-IV aGVHD was reported as similar in both PBSC and bone marrow recipients. Other factors supposed to increase risk for GVHD are older age of both recipient and donor, sex mismatch specifically a multiparous female donor into a male patient, a malignant diagnosis as opposed to a nonmalignant one, and a higher intensity conditioning regimen. Gene polymorphism affecting IL-1, IL-6, IL 10, TNF, TGF-β and IFN-γ have all been implicated in the incidence and severity of GVHD both in experimental models and immunogenetic analysis of retrospective clinical data [131] .

The pathophysiology of aGVHD has been described as a three phase model: Tissue damage from conditioning regimen, activation and proliferation of donor T cells, and subsequent damage to host cells [132]. The conditioning regimen related tissue damage leads to dysregulation of cytokine release with secretion of interferon-γ (IFNγ), inteleukin-1 (IL-1) and tumor necrosis factor-α (TNFα). Release of these cytokines may increase the recipient tissue expression of MHC antigens and exacerbate the graft versus host activity of donor T cells. Intestine and liver are the tissues especially susceptible to damage under stress of myeloablative regimens and in relation to this, patients with higher volumes of diarrhea at the time of the preparative regimen have been proposed to have a higher likelihood of aGVHD [133]. In the second phase, both recipient and donor antigen presenting cells as well as inflammatory cytokines trigger activation of donor derived T cells that expand and differentiate into effector cells. Once T cells have proliferated and been activated, the third phase ensues and T cells release inflammatory cytokines that are IL-2, IFNγ, and TNFα, leading to both indirect and direct damage to host tissues. In addition to cytotoxic soluble mediators, direct cell mediated cytotoxicity as being perforin-granzyme-B-mediated cytolysis and Fas-Fas ligand mediated apopitosis are important pathways in pathogenesis [134,135]. This three phase event leads to distinct clinical manifestations affecting the skin, gut and liver each of which can be semiquantitated and thereby staged that is important to assess the severity and to suggest treatment intensity.

In 1974, Glucksberg [136] published the first aGVHD classification and each organ is staged from 0 to 4.

Because of the system's limitations, it was modified in 1994 at the Keystone conference (Table 1) [137]. Although staging of gut in pediatric group was not discussed at the conference, many centers have defined staging of gut GVHD based on volume of diarrhea per kilogram of body weight. Acute GVHD is a clinical diagnosis but since many of the symptoms are non-spesific, histological confirmation may be useful especially if the symptoms are atypical.

The major emphasis in GVHD has been on prevention since the prognosis, if developes, is dismal. The combination of a calcineurin inhibitor [cyclosporine (CsA) or tacrolimus] with short course of methotraxate (MTX) has been accepted as standart regimen resulting in a reasonable balance of GVHD and graft versus leukemia in matched sibling transplants after ablative conditioning. In a recently published meta-analysis evaluating the benefit of different prophylactic regimes, it was shown that MTX-tacrolimus was superior to MTX-CsA in the reduction of aGVHD and severe aGVHD [138]. However in a prospective unrelated donor transplant study conducted in pediatric age group, the incidence of grade III/IV was found similar in patients using CsA or tacrolimus for prophylaxis [139]. Since there is concern about MTX further delaying engraftment in cord blood transplantation, MTX sparing regimens, that is substituted by methylprednisolone(MPD)or mycophenolate mofetil, have been proposed in unrelated cord blood transplantation. However, time to engraftment was found similar in two cord blood transplantation studies receiving CSA/ MPD [140] or CSA/MTX [141]. Patients receiving mismatched or unrelated donor grafts are usually in need of more intensive immunosuppression. Methods of ex vivo T cell depletion (TCD) as well as pharmacologic in vivo TCD have been used. In general, these methods reduce aGVHD but increase the risk of infection and the incidence of relapse.

Once GVHD occurs, first line therapy generally includes a continuation of prophylactic immunosuppression and adding methylprednisolone. The Group for Marrow Transplantation has carried out prospective studies to identify the best strategy for the treatment of aGvHD [142-144]. The conclusions of these studies are the following: more aggressive first line therapy is not beneficial. In particular, there were no differences in terms of TRM between high doses (10mg/kg/day) versus low doses (2mg/kg/day) of MPD, or between patients treated with ATG versus patients who received average doses (5mg/kg/day) of MPD. In addition patients who showed early response to low doses of steroids had significantly lower TRM, while the non-early responders were eligible for alternative immunosuppressive therapies. Approximately 50% of patients with aGvHD can be treated with first-line treatment, but if it is resistant to corticosteroids, prognosis becomes dismal. New drugs, new Abs or increased immunosuppression, and immunomodulatory procedures such as ECP may induce remission of GvHD, but problems involving infections or side effects still exist. Cellular therapy seems promising, as does the possibility of inducing immunotolerance. Although promising results have been observed with these interventions, none have yet shown a definitive improvement in overall survival for patients with steroid refractory a GVHD.

Chronic GVHD, although less common in children, represents a major cause of mortality. Zecca et al [145] reported the cumulative probability of developing limited and extensive cGVHD as 17% and 11%, respectively and identified older age of recipient and donor, female donor, malignant disease, TBI and previous aGVHD as the risk factors in pediatric patients. The basic pathophysiology of chronic GvHD is not as well defined as that of aGVHD. Both donor derived alloreactive T cells similar to aGVHD and also autoreactive T cells that arise in the allogeneic setting due to thymic injury from acute GvHD, that prevents the deletion of autoreactive clones appear to play role [146,147]. The widespread deposition of collagen is characteristic of many of the clinical findings in cGVHD and the clinical course often looks like other well-described auto-immune diseases. A combination of CsA and prednisolone has been the standart frontline therapy for cGVHD for almost 20 years [148]. However therapy for cGVHD in addition to clinical consequences itself are associated with significant risks, thus, patients may get benefit from risk stratification by adjusting therapies and reserving the more immunosuppressive and experimental interventions for those at high risk. Three risk factors were identified to be associated with non-relapse mortality at cGVHD diagnosis that were thrombocytopenia (<100.000 /mm3), extensive skin involvement and progressive-type onset in which aGVHD evolves to cGVHD without interruption of signs [149]. There is a need for randomized prospective trials to investigate the addition of other immunosupression to upfront therapy in the light of prognostic factors.

Non-Infectious Complications

Gastrointestinal and liver complications

Gastrointestinal toxicity is the most commonly seen regimen-related toxicity in HSCT recipients. Alkylating agents affect the basal layer of the mucosal lining leading to mucositis, that is the single most debilitating side effect from the patients' perspective, and also diarrhea, nausea and vomiting [150]. As this toxicity progresses, it may lead to colitis, typhlitis and esophagitis. Keratinocyte growth factor has been used to prevent mucositis in adults

but studies in children are warranted [151]. Glutamine (Gln), a conditionally essential amino acid during severe catabolic states, has been shown to have favorable effects in reducing the severity of mucositis and strong consideration is recommended to include oral glutamine supplementation as a routine part of supportive care of SCT patients [152,153]. Most of the patients develop anorexia, reduced caloric intake and weight loss requiring enteral or parenteral nutrition. Parenteral nutrition continues to be the primary avenue for nutrition support despite growing evidence that enteral feedings can be successfully administered [154]. Dental abnormalities including serious gingivitis, parodontal involvement, hypoplasia, root anomalies, tooth dwarfism, incomplete calcification, agenesis and so on are also common and young age at the time of transplantation is a risk factor for a substantial rate of dental complications. The prolonged reduction of salivary gland secretion occurring especially after TBI or as a common finding in cGVHD, can predispose to oral complications. The damage to salivary glands may be permanent after radiation.

The liver is a frequent target of toxicity in HSCT recipients. Acute and chronic GVHD, veno-occlusive disease, iron overload as a consequence of multiple transfusions, chronic hepatitis, opportunistic infections and reactivation of viral hepatitis are the most frequent acute and chronic liver diseases occurring after HSCT. Veno-occlusive disease (VOD), recently termed as sinusoidal obstruction syndrome (SOS) is a complication characterized by jaundice, fluid retention and painful hepatomegaly. VOD most often occurs within the first 20 days after HSCT although some regimens are associated with a delayed onset or even a bimodan presentation [155]. The incidence of VOD in children ranges between 27 and 40% [156,157]. The pathophysiology of SOS includes endothelial damage , sinusoidal fibrosis in zone 3 of the liver acinus, microthrombus, fibrin deposition and ultimately hepatic necrosis. Conditions that have been identified as risk factors are as follows: Age below 5 years, haploidentical or unrelated donor, diagnosis of osteopetrosis or HLH, second transplant with myeloablative regimen, earlier abdominal irradiation, hepatic cirrhosis, prior treatment with gemtuzumab, busulphan based conditioning regimens [158]. Diagnosis relies on sets of clinical criteria namely Seattle and Baltimore criteria. Complimentary studies like ultrasound scan or some biological markers (decrease in antithrombin III, protein C and S, increase in plasminogen activator inhibitor-I, procollagen type IIIC) may be used to confirm the diagnosis [159-162]. Bimodal presentation of the disease, doubling of serum creatinine, high levels of transaminases, portal vein thrombosis and decreased oxygen saturation have been proposed to correlate with poor prognosis [69]. No standard effective therapy is currently available but defibrotide has been reported to be useful in several studies both for the prophylaxis and therapy of VOD [159-163].

Hepatitis B virus (HBV) carrier children or the ones with resolved infection (HBsAg negative, AntiHBs positive, anti-HBc positive) are at risk of developing HBV reactivation after transplantation. Preemptive therapy with lamuvidine is recommended in pediatric HBV carriers to decrease the chance of severe hepatic complications [164]. Also HBV naïve patients should be immunised against hepatitis B, as should hematopoietic stem cell donors [165]. Hepatitis C virus (HCV) is known to be associated with transient hepatitis in the immediate post-transplant period, and a potential risk factor of veno-occlusive disease (SOS). Long-term HCV-infected survivors, on the other hand, have been shown to have higher risk of earlier cirrhosis, leading to greater morbidity and mortality [166]. Children with iron overload are also at risk for short and long-term hepatic complications necessitating interventions to reduce iron burden either with phlebotomies or in combination with iron chelating agents after transplantation [167,168].

Gastrointestinal and liver cGVHD in pediatric recipients are 24 and 28%, respectively [169]. Dysphagia, pain, weight loss are the most common manifestations and mucosal erytheme, lichen-type hyperkeratosis, ulcerations of the mouth and increase levels of transaminases, gamma glutamic transpeptidase and conjugated bilirubin are the usual findings.

Pulmonary complications

Pulmonary complications, although less frequent in pediatric HSCT recipients, remain an important concern accounting for a significant percentage of morbitiy and mortality during the first 100 days after transplant [170-172]. Early complications occurring in the first 100 days include pulmonary edema, bacterial infections, pneumocystitis infections, fungal infections, viral infections having the greatest threat and also idiopathic pneumonia syndrome (IPS) and diffuse alveolar hemorrhage (DAH).

IPS is defined as diffuse lung injury following HSCT for which an infectious agent etiology has not been identified [172]. This happens around day 21 and results from a diversity of lung insults including the toxic effects of the conditioning, immunologic cell mediated injury, inflammatory cytokines and probably, occult pulmonary infections. Clinical findings are fever, non productive cough, tachypnea, hypoxemia, diffuse alveolar or interstitial infiltrates on x-ray. Although there is no spesific treatment, corticosteroids are often used with some improvement and also some successes have been defined with antiTNF MoAB.

DAH, very similar to SOS in the pathogenesis but at the lung level,is usually diagnosed within the first 30 days after transplantation. The main clinical manifestations are dyspnea, tachypnea, non-productive cough, and hypoxemia with focal and diffuse infiltrates on chest X-ray or CT scan and with increasingly bloody samples during bronchoalveolar lavage (BAL) not attributable to infection (absence of pathogens in BAL) [173]. High dose methyl prednisolone was shown to improve survival and was considered as the treatment of choice [174]. However a poor outcome not modified by steroid treatment has been necessitated to evaluate the possible role of other agents like recombinant FVII a, cytokine antagonists and anti-inflammatory agents.

Late pulmonary complications include both infectious and non-infectious causes. Uderzo et al [175] reported 35% cumulative incidence of lung failure in children at 5 years and a chronic GVHD is the main risk factor implicated in reducing lung function . Screening for pulmonary abnormalities is strongly recommended by the EBMT/CIBMTR/ASBMT guidelines even in the asymptomatic patients and pulmonary function testing (PFT) was proposed as the most reliable method for detection and follow-up of late-onset non-infectious pulmonary complications (LONIPC) [176,177]. Based on PFT, LONIPC can be evaluated in two groups as obstructive or restrictive type. Obstructive respiratory insufficiency shows decrease forced expiratory volume in 1 second (FEV1) (≥80 %) with a normal forced vital capacity (FVC) resulting in decrease in FEV1/FVC ratio (<70%), as a result of obstruction of small airways, mainly because of cGVHD in allogeneic HSCT recipients. Restrictive respiratory syndrome, on the other hand, shows decreased FVC (<80%) and FEV1/FVC ratio is ≥70 %, mainly related with conditioning regimen including TBI. LONIPC that arise beyond 3 months after allogeneic HSCT include bronchiolitis obliterans (BO), bronchiolitis obliterans with organizing pneumonia (BOOP) and idiopathic pneumonia syndrome (IPS). Obstructive lung diseases are frequently associated with Ig G and Ig A deficiency, chronic GVHD, infections, use of methotreaxate, and TBI, both the total radiation dose and the schedule affecting the outcome. Considering that we are lacking optimal therapies for LONIPCs, strategies aimed at the prevention of LONIPCs should be attempted [178].

Renal complications

Nephrotoxicity in HSCT recipients is commonly multifactorial. Multiple drugs used throughout the transplantation course, cell lysis products from a prior preserved stem cell collection and sepsis may cause renal impairment. The incidence of acute renal failure (ARF) immediately after HSCT in pediatric patients is between 25% and 50%, with 5%-10% of children requiring renal replacement therapy [179-183]. The doubling of serum creatinine was found to be associated with a twofold increase in mortality, and the need for dialysis predicted a mortality rate of 84%–88% [184,185]. Drugs such as cyclosporine or mitomycin C have been associated with thrombotic microangiopathic anemia, a syndrome that may also be caused by certain chemotherapatic agents, irradiation and infections [186]. Thrombotic microangiopathy usually develops around day +60, but early and late episodes have been described. Toxicity of conditioning regimen with other initiative factors, not clearly defined yet, produces a generalized endothelial dysfunction and intravascular platelet activation leading to formation of platelet rich thrombi withinin microcirculation. It is characterized with anemia, thrombocytopenia, fever and and/or neurological disturbances and almost universally with renal insufficiency, putting the disease into the category of hemolytic uremic syndrome and/or thrombotic thrombocytopenic purpura. Removal of immunosuppressive therapy and supportive measurements are recommended [187].

Hemorrhagic cystitis (HC) represents a common cause of morbidity after HSCT with an incidence ranging between 1 and 25%, if all prevention treatments are applied [158]. It may occur early (within 72 hour) after transplantation or later, after the first month, produced either by direct toxicity of the conditioning agents on the urothelium or by viral pathogens mainly human polyomavirus type BK or JC, adenovirus or CMV, affecting urinary tract, respectively. Hyperhydration and the use of mesna are effective preventive approaches.

The incidence of late HSCT nephropathy in children ranges between 17 to 28% with onset within a year after transplant [183,188].TBI, particularly in combination with immunosupppressive agents, represents the main cause of chronic renal failure following HSCT [189]. Based on this observation, shielding of the kidneys in patients at high risk of developing GVHD who receive TBI doses greater than 12 Gy has been suggested [190].

Cardiac complications

Cardiotoxicity can present as acute or late onset and may be either asymptomatic or progressive with clinical symptoms. The clinical manifestations of cardiac damage include left ventricule dysfunction, abnormalities of the electrical pathways that conduct impulses, pericardial or blood vessel diseases [191,192] Most patients have some cardiac dysfunction during or immediately after HSCT and as many as 50 % have persistant abnormalities, hopefully, usually subclinical. The risks for long-term cardiac complications after HSCT are mainly related to previous

treatment before HSCT, particularly anthracycline therapy at doses >250-300 mg/m^2, myeloablative doses of cyclophosphomide more than 150 mg/kg, radiation to chest and iron overload [193]. Almost all conditioning regimens contain myeloablative doses of cyclophosphomide with a potential risk of hemorrhagic myocarditis as well as TBI (especially without fractionation) and high dose steriods further enhancing toxicities. Cardiotoxicity increases over time, even without further therapy for the underlying disease for which transplantation was done [193]. Possible explanations for this observation include loss of reserve heart muscle, early progression of atherosclerosis and also presence of chronic GVHD. Although uncommon, findings consistent with cGVHD have been identified in the myocardium. Heart attack,even complete heart block presumably secondary to cGVHD have been reported.Asymptomatic patients transplanted during childhood may become symptomatic during rapid growth, following initiation of vigorous exercise prorammes and also during pregnancy, mainly because of marginal reserves or diminished compensatory mechanisms and more close follow up during such periods should be recommended.

Endocrinological late complications

One of the most frequent late effects of HSCT is thyroid dysfunction due to chemotherapy, radiotherapy or cGVHD . Radiotherapy is the most important risk factor. The irradiation dose and number of fractions were found to correlate with the severity of thyroid dysfunction. Compensated hypothyroidism is known as the most frequent thyroid complication up to 30%. Approximately 15% of the patients develop overt hypothyroidism [194] The incidence is lower in patients who received fractionated TBI even lower in patients conditioned with chemotherapy alone. Young adults transplanted during childhood and adolescence should be checked periodically to detect thyroid illness. Adrenal insufficiency is another important endocrine problem that occurs due to steroid therapy.

Testicular or ovarian failures are usually secondary to conditioning regimen. Radiotherapy and busulphan may cause gonadal damage as conditioning regimen in pre-transplant period [1195,196]. Hypergonadotropic hypogonadism develop in most of these patients and recovery is rare. Sperm banking is the only method for preserving fertility in sexually mature adolescent male patients. However it is impossible to apply in a prepubertal child. Newer technologies such as testis sperm extraction or intracytoplasmic sperm injection may be an option in males [194]. The usual TBI doses for conditioning induce ovarian damage in almost all girls older than 10 years and half of the girls younger than 10 years [194]. Conditioning with BU also causes ovarian failure in almost all the cases [197]. Sex hormone replacement therapy with estrogens and progestin may helpful in women with ovarian failure.

Secondary malignancies

Prolonged follow-up of the transplant patients has arised another concern, that is second malign neoplasms, with a increased risk up to 20 years after transplantation in childhood [198]. Younger age at transplantation and genetic predisposition have been proposed as risk factors for second neoplasms in addition to previous radiotherapy, TBI and/or chemotherapy (especially alkylating agents) and cGVHD (oropharyngeal cancer and skin) [176,199,200]. Skin, oropharyngeal, thyroid and breast cancers predominate. Whether the risk is higher in these patients than in patients undergoing standard high-dose chemo- and/or radiotherapy has not yet been well defined. Secondary lymphoproliferative diseases and haematological malignancies include myelodysplastic syndrome, acute myeloid leukaemia and post-transplant lymphoproliferative disorder (PTLD) that is associated with EBV. The risk factors for PTLD include type of graft (mismatched related donor), primary immunodeficiency, use of ATG, T-cell depletion and aGvHD>II grade.

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