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Hematopoietic Stem Cells Therapeutic Applications

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1. Introduction

Hematopoietic stem cell transplantation (HSCT) has become an established treatment for malignant hematological diseases, solid malignancies and non-malignant diseases (figure 1). Newer indications for HSCT have emerged because of better understanding of human immunology, tumor biology and immunotherapy (table 1). Novel approaches have resulted in increase number of transplants as well as significant reductions in the morbidity and mortality associated with HSCT. These include more suitable donors with the addition of unrelated cord blood units (single & double) and partially matched family members; and novel conditioning regimens (reduced & non-myeloablative) that allow patients with significant co-morbidities to undergo transplantation. On the other hand, the introduction of alternative therapies, such as imatinib (tyrosine kinase inhibitor) for chronic myelogenous leukemia (CML), has challenged well established indications. This chapter summarizes the current indications for HSCT in pediatrics and address recent clinical developments in the field of HSCT.
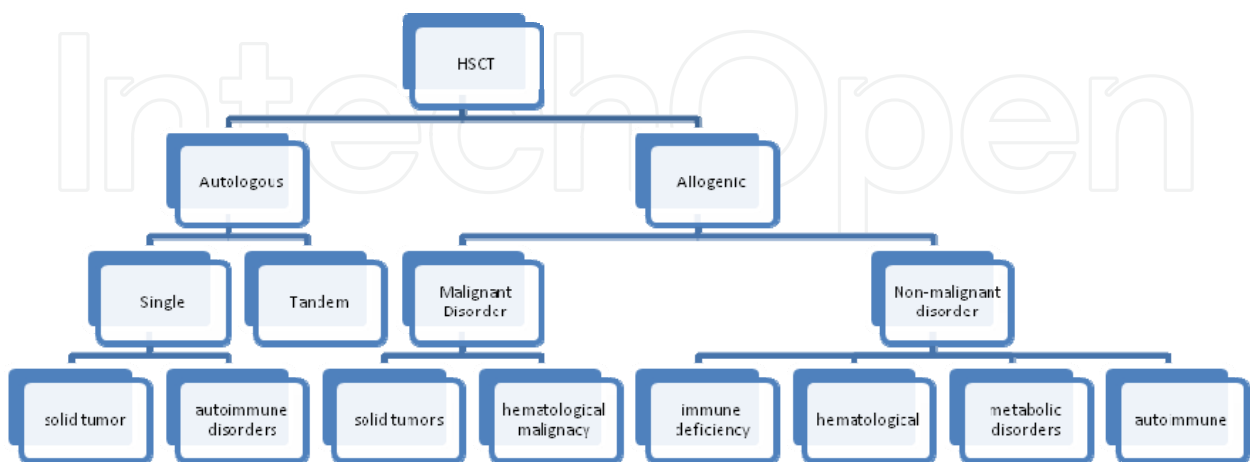

Fig. 1. Indications for HSCT

ALL	Immunodeficiency with hyper IgM
• In CR 1[a]	Leukocyte adhesion deficiency
• In CR 2	Omenn syndrome
• In CR 3 or further	Chediak-Higashi syndrome
AML in CR I or further	X-linked lymphoproliferative disease
CML	Kostmann syndrome
Myelodysplastic syndromes	Chronic granulomatosis disease
Hodgkin and non-Hodgkin lymphoma	Glanzmann thromboasthenia
Selected types of solid tumors[b]	Bernard-Soulier syndrome
Bone marrow failure syndromes (acquired & congenital)	Familial hemophagocytic lymphohistiocytosis
	Selected types of mucopolysaccharidoses,
Thalassemia major	Selected types of peroxisomal and lysosomal
Sickle cell disease	disorders
Infantile malignant osteopetrosis	Selected types of life-threatening autoimmune
SCID	disorders resistant to conventional treatments

Abbreviations: ALL= acute lymphoblastic leukemia; AML= acute myeloblastic leukemia;
CML= chronic myeloid leukemia; CR1, 2, 3= first, second and third complete remission;
SCID= severe combined immunodeficiency.

[a]Patients at high risk of recurrence (that is, t (9; 22) or t (4; 11); T-ALL with poor prednisone response, high levels of minimal residual disease).

[b]Stage IV neuroblastoma, renal cell carcinoma, very high risk Ewing sarcoma.

Table 1. Main Indications to allogeneic hematopoietic SCT in childhood

2. Indications for hematopoietic stem cell transplantation (HSCT) in pediatrics

There are two types of HSCT: autologous and allogeneic. Autologous HSCT consists of removal, storage and reinfusion of patients own hematopoietic stem cells as a way to restore the patient's depleted bone marrow after high dose myeloablative therapy (figure 2). Allogeneic HSCT consists of transferring both immature and mature blood cells to a patient from the bone marrow, peripheral blood or umbilical cord blood of a sibling, relative or an unrelated donor (figure 2) as a way to restore the patients bone marrow with a new immune system after a conditioning regimen (non-myeloablative or myeloablative chemotherapy). The success of an allo-HSCT is limited by the toxicity associated with the conditioning regimens, graft versus host disease (GVHD) and the development of opportunistic infections. New concepts and interventions over the last two decades have resulted in reduction of the morbidity and mortality associated with allo-HSCT. These include the utilization of reduced intensity regimens, more effective GVHD prophylaxis, new sources of progenitor hematopoietic stem cells, donor lymphocyte infusions and better prophylaxis and treatment for infectious diseases.

The decision to transplant or not to transplant should be determined on individual basis and several factors should be considered including the disease status, age, prior treatments and responses, donor availability and evolving alternative therapies.
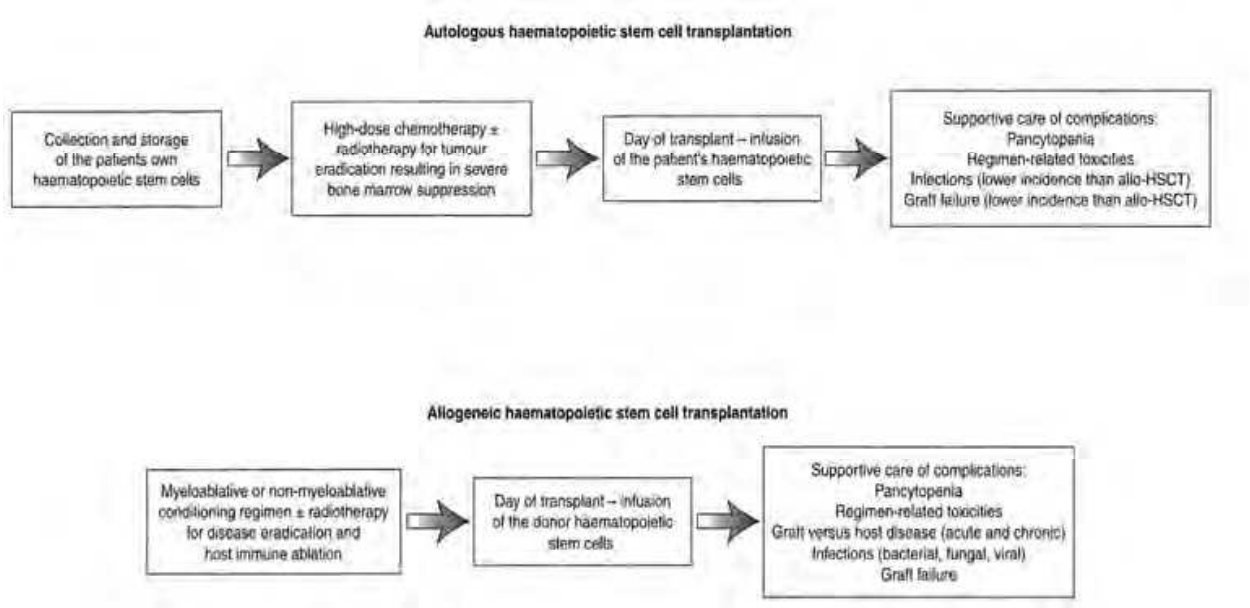
Fig. 2. Major Key Steps of HSCT.

2.1 Leukemias

2.1.1 Acute myeloid leukemia (AML)

Despite intensive chemotherapy, less than half of all patients with AML will survive in the long term (Creutzin, 2005; Gibson, 2005). Treatment outcome of pediatric AML is not as favorable as in ALL. AML treatment failure is due primarily to disease recurrence, although treatment-related mortality remains an important cause of treatment failure. Improvement in AML outcomes have been due primarily to intensification of therapy and improved supportive care guidelines. In AML, treatment intensity is an important determinator of outcome, and many studies have focused on the role of HSCT as post-remission intensification, utilizing both autologous as well as allogeneic HSCT. Allogeneic HSCT may provide a graft versus leukemia effect in pediatric AML. This is supported by a study from Bader et al that showed that preemptive immunotherapy following HSCT in patients with increasing (mixed chimerism) may lead to improved outcome. In another study Neudorf et al reported that children treated with allogeneic-HSCT in the children's cancer group 2891 study who developed acute graft versus host disease (GVHD) had fewer relapses (Bader, 2004; Neudorf et al., 2004).

The American society of bone marrow transplant position statement for the treatment of AML in children indicates that allogeneic HSCT should be recommended in the first complete remission because transplant has better overall survival and leukemia-free survival compared with chemotherapy alone (ASBMT, 2007; Oliansky, 2007). However, the role of allogeneic-HSCT in complete remission one (CR1) is declining because of the better outcome with modern multiagent chemotherapy and better methods of identifying patients that have low risk features at diagnosis and therefore are more likely to be cured with conventional chemotherapy. Recent AML trials (MRC-AML-12 & AML 0531) have shown that prognostic factors like cytogenetic and response to induction therapy are highly predictive of determining patients that are high risk at diagnosis and therefore would benefit from allogeneic-HSCT in CR1, while sparing lower risk patients the potential toxicities associated with an allogeneic-

HSCT (Ljungman, 2009). Recent analysis by several cooperative groups has now identified relapse risk group parameters based on cytogenetics abnormalities and early response to treatment : Low risk is defined as inversion (16)/t(16;16) or t(8,21). Down syndrome patients are also included in this low risk group; High risk is defined as monosomy 7, monosomy 5,5q deletions, or greater than 15% blasts at the end of induction I but who achieve complete remission after induction II, or high FLT3-ITD alleic ratio; Intermediate risk includes all other patients with no cytogenetic information available. This risk group is used to determine which patients should receive a HSCT in CR1.

Currently, HSCT is not recommended as frontline therapy for low-risk patients with AML in CR1, as they have an overall survival of 60% with conventional chemotherapy and HSCT has not been demonstrated to improve outcome for patients in CR1 (Gibson, 2005). HSCT is also not indicated for Myeloid Leukemia of Down Syndrome because HSCT is associated with excess toxicity with or without therapeutic gain (Lange et al., 1998). In addition, HSCT is also not indicated for acute promyelocytic leukemia (APL) due to excellent cure rates with conventional chemotherapy. However, for the few patients with APL who relapse or have persistent minimal residual disease, the prognosis is less favorable and HSCT might be a recommended choice (Oliansky et al., 2007). Allogeneic-HSCT from an HLA-identical sibling is an option for patients defined as intermediate risk. Allogeneic-HSCT from an HLA-identical sibling or an unrelated donor in CR1 is indicated for children with high risk AML including infant AML, therapy-related AML and children with M0 or M7 as it was proven to be more efficient than chemotherapy in some comparative studies with an event free survival ranging from 55 to 72% (Gibson, 2005). Regarding the use of haploidentical HSCT for AML, results in children with AML undergoing haploidentical HSCT have shown some effect of natural killer alloreactivity, suggesting that haploidentical HSCT may have a role in early phase very high AML patients (Marks et al., 2006).

HSCT also has an important role in the treatment of relapsed AML because outcome is poor with chemotherapy alone. Marrow transplantation in early first untreated relapse or CR2 results in a two-year EFS rate of 30-40%(Besinger,1995; Schimitz, 1998). Analyzes that attempt to compare outcome based on treatment have shown a survival advantage for patients who receive marrow transplants compared with chemotherapy alone, particularly for patients with longer first remission (Besinger, 1996).Therefore, allogeneic-HSCT from an unrelated or related donor is indicated in children with relapse AML in CR2, as it may provide long-term survival, particularly those in first relapse that are in remission.

Autologous HSCT has been used as consolidation in children with AML in CR1 after induction therapy and represents a valid alternative for high-risk children lacking a matched sibling donor. Nevertheless, results of pediatric studies comparing autologous HSCT with chemotherapy are conflicting. The use of peripheral blood stem cells in children with AML given autologous HSCT is infrequent. Further prospective clinical trials are needed to address the pivotal clinical question of whether autologous HSCT is better than chemotherapy or allograft as consolidation treatment for childhood AML in first CR (Miano et al., 2007).

2.1.2 Acute lymphoblastic leukemia (ALL)

ALL is not a uniform disease, but consists of different subtypes with different clinical prognostic and cytogenetic features. The prognosis of childhood ALL has improved

dramatically over the past quarter of a century. Currently, over 2500 children in the United States are diagnosed each year with ALL and almost 95% attain a clinical remission after three or four drug induction chemotherapy (Clavell, 1986; Pui, 1998; Reiter, et al., 1994; Rivera, 1993). Over 83% of children with newly diagnosed ALL treated with multi-agent chemotherapy with or without clinical radiotherapy are alive and disease free at 5 years (Gaynon, 2000; Silverman, 2001; Vilmer, 2000).

Despite recent advances in the diagnosis and treatment of childhood ALL, there are several subpopulations of patients that have molecular biological markers or chromosomal abnormalities and biological factors that include poor prednisone response and resistance to initial chemotherapy including persistence minimal residual disease, that makes them very high risk of failing current multi-agent chemotherapy regimens. These very high risk patients require alternative treatment strategies to prevent progression and/or relapse of their disease (Kersey, 1997; Pui,1995). Table 2 defines the very high risk ALL patients.

The indication for HSCT from a match sibling or an unrelated donor for children with ALL in CR1 is limited to the subpopulation of patients that have clinical and biological features that identifies them as very high risk of relapse, as most studies quote an event-free survival (EFS) of less than 50% and a relapse rate of up to 50% (Reiter et al., 1994; Rivera, 1993). Children's oncology group conducted a clinical research study from 1993 to 1996 to investigate the toxicity and efficacy of HSCT in newly diagnosed children with very high risk features of ALL at diagnosis and/or during initial induction chemotherapy and their findings support the current indication of HSCT for very high risk ALL in CR1, especially patients with primary induction failure and Philadelphia chromosome positive ALL (Satwani, 2007).

HSCT should also be considered as an option for relapse ALL. The decision to perform an allogeneic matched related or unrelated donor HSCT for patients with relapse ALL depends on many factors which can be considered strong predictors of outcome as suggested from a number of literature reports. Different sites of relapse and the duration of first remission may be the most important factors predicting outcome after a first relapse. Patients with late relapse (over 6 months from therapy withdrawal) may have relatively good outcome with conventional chemotherapy alone (Borgmann et al., 1995; Ritchey, 1999; Uderzo et al., 1990). In contrast, children who relapse (isolated/combined medullary) during therapy or within 30 months of diagnosis seem to benefit more from HSCT than chemotherapy with an event-free survival rates of 40-50% reported for patients in CR2 who underwent a HSCT (Kawakami et al.,1990).

It has been difficult to compare outcomes of patients treated with chemotherapy or HSCT, since patient populations are not necessarily equivalent. Patients with aggressive disease die earlier and may not be included in studies of marrow transplantation, resulting in selection bias (Tichelli et al., 1999). To address this question, matched-pair analyses have been performed for ALL CR2 patients treated with chemotherapy or HSCT (Dreger et al., 1997; Novotny et al., 1998). For patients with early first relapse, HSCT resulted in significantly better EFS rates at 5 years compared with chemotherapy alone (40% vs 17%; p<0.001) (Novotny et al., 1998). Marrow transplantation was associated with a reduced risk of relapse that was not negated by increased treatment related deaths. The difference between chemotherapy and HSCT for patients who experienced a late marrow relapse (45% DFS vs

65%) (Chessells et al., 1986; Hoogerbrugge et al., 1995) was evident but not statistically significant.

Another factor to consider when deciding whether HSCT is an option for relapse ALL is the phase of leukemia at the time of transplant because it is also highly predictive for the risk of leukemia relapse and death from non-relapse causes. In particular, patients transplanted in relapse with over 30% circulating blast, have very poor survival following HSCT (Kessinger, 1989). Patients transplanted in remission compared to those in relapse have a two to five fold reduction in risk of relapse (p=0.0001) (36).

In summary the current opinion is that the earlier the relapse the more difficult is to obtain and maintain a second complete remission, so HSCT should be consider as an elective therapeutic option in order to eradicate a resistant disease. Relapse patients who fail to achieve remission prior to transplant have very poor outcome, so HSCT should not be undertaken.

Any one or more of the following:

- Cytogenetics
  t(9;22) (q34, q11) or BCR-ABL molecular rearrangement
  t(4;11) (q21, q23) or 11q23 molecular rearrangement
  Hypodiploidy (≤44 chromosomes)
- Age ≥10 years and WBC ≥200 x10^9/L
- Induction failure (day 28 M2 or M3 BM)
- Infant ALL (2-12 months) with any one or more of the following:
  CD10 negative (CALLA) ALL phenotype
  WBC ≥100 x10^9/L at diagnosis
  Day 14 M2 or M3 BM

Table 2. Ultra High-Risk Criteria of Childhood ALL in CR1.

2.1.3 Chronic myelogenous leukemia (CML)

CML is rare in childhood and accounts for less than 10% of all childhood leukemia. The treatment of CML has undergone dramatic changes in recent years. Before introduction of HSCT, the standard treatment approach for chronic phase CML was single-agent chemotherapy such as busulfan, hydroxyurea and interferon-alpha, however, treatment rarely produced a true complete remission. After 1980's, allogenic-HSCT was introduced as the only curative therapy for patients with CML. Five large multi-institutional retrospective studies have shown a high rate of long-term disease free survival (55-75% after myeloablative allogeneic HSCT), but survival was accompanied by significant treatment-related mortality, especially when unrelated donor allografts were used (Creutzig, 1996; Cwynarski et al., 2003; Millot et al., 2003; Weisdorf et al., 2002). From the 1980's to 2000, allogeneic HSCT was the treatment of choice for younger patients in first chronic phase if an HLA-matched donor was available. Before 1999, CML was the most frequent indication for allogeneic HSCT worldwide. With the approval of imatinib by the FDA in 2001, this tyrosine kinase inhibitor soon became the frontline therapy for newly diagnosed CML patients and transplant rates in CML dropped quickly worldwide (Muramatsu et al., 2010).

Dramatic responses to oral imatinib administration were observed in adult patients with CML (Druker et al., 2001; Hughes et al., 2003). However, clinical experience with imatinib in the pediatric population is limited. Several studies have shown that treatment with imatinib has resulted in prolonged molecular response with limited drug toxicity with comparable results with those in adult patients (Millot et al., 2006). Imatinib is now implemented in the primary treatment regimen for children, but the paucity of evidence on its ability to result in permanent cure and the potential complications that may arise from long-term treatment with imatinib have prevented imatinib from superseding HSCT as the primary means of curative treatment in children. The results of allogeneic HSCT in children with CML are similar to those observed in adults; HSCT-related complications such as transplant-related mortality and graft versus host disease remain significant challenges.

There is a general consensus for the need for HSCT in patients with imatinib resistance or those with advance-phase (accelerated and blast phase). (Table 3). However, issues such as when to undertake HSCT in chronic-phase CML pediatric patients or how best to treat patients who have relapsed after HSCT are still controversial. When considering HSCT vs imatinib in pediatric CML patients in early chronic phase, one must consider that the objective for treatment of childhood CML is not palliation, but cure. Hence, the possible adverse effects that stem from long-term tyrosine kinase weigh more heavily in the childhood CML population. HSCT still remains an important treatment option especially for younger patients with CML depending on physician and patient preferences. As a result of multiple clinical trials in adults that have documented great results with the use of imatinib in CML in chronic phase (87% of patients treated with imatinib showed complete cytogenetic response at 18 months with 3.3% disease progression) (O'Brian et al., 2003), this results have been applied to children, and imatinib is now also the front-line treatment for childhood CML.

World Health Organization (WHO) Criteria	International Bone Marrow Transplant Registry Criteria
Accelerated phase	Accelerated phase
1) Persistent or increasing WBC (>10×10⁹/L) and/or persistent or increasing splenomegaly	1) Leucocyte count difficult to control with hydroxyurea or busulfan
2) Persistent thrombocytosis (>1,000×10⁹/L) uncontrolled by therapy	2) Rapid leucocyte doubling time (<5 days)
3) Persistent thrombocytopenia (<100×10⁹/L) unrelated to therapy	3) PB or marrow blasts ≥10%
4) Clonal cytogenetic evolution occuring after the initial diagnostic karyotype	4) PB or marrow blasts and promyelocytes ≥20%
5) Peripheral blood (PB) basophils ≥20%	5) PB basophils and eosinophils ≥20%
6) 10-19% myeloblasts in the PB or bone marrow (BM)	6) Anemia or thrombocytopenia unresponsive to hydroxyurea or busulfan
Blast phase	7) Persistent thrombocytopenia
1) Blasts equal or are greater than 20% or the PB WBC or the nucleated cells of the BM,	8) Clonal evolution
or	9) Progressive splenomegaly
2) Extramedullary blast proliferation	10) Development of myelofibrosis
3) Accumulation of blats occupy focal but significant areas of the BM	Blast phase
	1) ≥30% blasts in the PB, marrow, or both
	2) Extramedullary infiltrates of leukemic cells

Adapted from Swerdlow, 2008; Speck, 1984.

Table 3. Definition of Accelerated Phase and Blast Phase Chronic Myeloid Leukemia (by WHO2008 and IBMTR Criteria)

The evaluation of the response to tyrosine kinase treatment is made through hematologic, cytogenetic and molecular testing (table 4). The overall evaluation should lead to a classification of treatment response as optimal, suboptimal or failure (table 5). For patients in early chronic phase who achieve an optimal response, the drug should be continued until allogeneic HSCT is undertaken. In those patients who fail to respond, second-generation tyrosine kinase inhibitors and HSCT need to be considered. In suboptimal responders, imatinib may be continued, possibly at a higher dosage, or second-generation tyrosine kinase inhibitors may be introduced (Lee & Chung, 2011) Prospective cooperative studies are needed to address this complex issue in young patients with CML.

Complete hematologic response

1. Complete normalization of peripheral blood counts with leukocyte count <10x10^9/L
2. Platelet count <450x10^9/L
3. No immature cells, such as blasts, promyelocytes, metamyelocyte
4. No signs or symptoms of disease with disappearance of palpable splenomegaly

Partial hematologic response
- Same as those for complete hematologic response, except for

1. persistence of immature cells or
2. platelet count <50% of the pretreatment count but >450xx10^9/L
3. persistent splenomegaly but <50% of the pretreatment extent

Cytogenetic response (in patients with complete hematologic response)

1. Complete response; No Ph-positive metaphase cells
2. Major response; 0-35% Ph-positive metaphase cells (complete+partial)
3. Partial response; 1-34% Ph-positive metaphase cells
4. Minor response; 35-90% Ph-positive metaphase cells

Molecular response

1. Complete molecular response; bcr-abl mRNA undetectable by RT-PCR
2. Major molecular response; $\geq$ 3-log reduction of bcr-abl mRNA

Adapted from Faderls, et al, 1999.

Table 4. Criteria for Cytogenetic and Hematologic Remission in CML.

| Time | Response | | | |
	Optimal	Suboptimal	Failure	Warning
At diagnosis	NA	NA	NA	Advanced phase
3 months	CHR	Less than CHR	No hematologic response ; Stable disease or disease progression No CyR (Ph+ > 95%)	
6 months	At least PCyR (Ph+≤ 35%)	Less than PCyR (Ph+> 35%)		
9 months	At least PCyR (Ph+≤ 35%)	Less than PCyR (Ph+> 35%)	No CyR (Ph+> 95%)	
12 months	CCyR	PCyR (Ph+, 1-35%)	Less than PCyR (Ph+> 35%)	Less than MMolR
18 months	MMolR	Less than MMolR	Less than CCyR	
Any time during treatment	Stable or improving MMolR†	Loss of MMolR, mutations in bcr-abl kinase domain	Disease progression, mutations in bcr-abl kinase domain	Disease progression, new clonal cytogen-etic abnormalities

Abbreviations: NA, not applicable; CHR, complete hematologic response, CyR; Cytogenetic response, PCyR; partial cytogenetic response, CCyR; complete cytogenetic response, MMolR; major molecular response, Ph+; philadelphia chromosome positive
†MMolR indicated a ratio of BCR-ABL1 to ABL1 or other housekeeping genes of ≤0.1% on the international scale.

Table 5. Recommendation for Definitions of Treatment Response to Imatinib Used in Early Chronic Phase. Modified from Suttorp M, et al, 2011 and Baccarani M et al, 2009.

2.2 Lymphomas

2.2.1 Non hodgkin's lymphoma (NHL)

Children suffering from NHL(Burkitt, lymphoblastic, diffuse large B cell and anaplastic large cell lymphoma) even with stages III/IV have excellent results when treated with first-line chemotherapy and radiation therapy. Long term EFS is between 60-90%(Cairo et al., 2007; Gerrad et al., 2008; Link, 1997; Patte et al., 2007). However, for refractory or recurrent Burkitt's, diffuse large cell and lymphoblastic lymphoma, the long term survival is only 10-20% (Atr, 2001; Cairo, 2003) In contrast, for refractory or recurrent anaplastic large lymphoma, up to 60% of patients may achieve long-term survival (53).

Several studies have shown that patients with chemosensitive recurrent diseases can achieve long-term disease free survival after HSCT. In a recent study by Thomas Gross published in 2010, he examined the role of HSCT for patients less than 18 years with the four different histologic subtypes receiving autologous or allogeneic HSCT (sibling & unrelated) from 1990-2005. To date this is the largest study done for refractory/relapse NHL. He concluded that EFS rates were lower for patients not in complete remission at HSCT, regardless of donor type. After adjusting for disease status, 5-year EFS were similar after allogeneic and autologous HSCT for diffuse large B cell (50% vs 52%), Burkitt's (31% vs 27% and anaplastic large cell lymphoma (46% vs 35%). However, EFS was higher for lymphoblastic lymphoma after allogeneic HSCT (40% vs 4% p<0.01). Predictors of EFS for progressive or recurrent disease after HSCT included disease status at HSCT and use of allogeneic donor for lymphoblastic lymphoma.

HSCT (auto & allo) can be effective in salvaging children and adolescents with refractory or recurrent NHL and results are superior if complete remission can be achieved prior to HSCT. Allogeneic donor is preferred for patients with lymphoblastic lymphoma.

2.2.2 Hodgkin's disease (HD)

Autologous HSCT is the standard therapy for patients with HD in first chemosensitive relapse or second complete remission (CR) as shown by two prospective randomized clinical trials (Linch et al., 1993; Schmitz et al., 2002)

Currently, there is no indication for autologous HSCT in first CR, even in patients with bad prognostic features at diagnosis (Federico et al., 2003; Proctor et al., 2002).

For primary refractory patients or for patients in chemorefractory relapse, autologous HSCT has only a small chance of inducing long-term remission (Lazarus et al., 1999; Sweetenham et al., 1999). As part of a clinical protocol for patients with resistant HD, autologous HSCT might be considered as an initial debulking therapy to be followed by an allogeneic HSCT as consolidation therapy (Carella et al., 2000).

Allogeneic HSCT has mainly been used as salvage therapy for multiply relapsed or refractory HD. A retrospective analysis indicates that reduced intensity conditioning allogeneic HSCT can improve the outcome of HD patients that relapse after an autologous HSCT (Thomson et al., 2008). Its impact in the long term outcome of these patients has still to be prospectively evaluated. HSCTs from HLA-identical sibling donors and well-matched unrelated donors give a similar outcome (Anderlini et al., 2008).

2.3 Myelodysplastic syndrome (MDS)

MDS is rare in children an allogeneic HSCT from a sibling donor or a well-matched unrelated donor is currently the only curative therapy that is available for children with de novo MDS, JMML or secondary MDS. MDS is a heterogeneous disorder, characterized by a clonal stem cell disease with ineffective hematopoiesis which is morphologically abnormal. MDS in children differs from MDS in adults, as children more frequently suffer from hypocellular MDS. De novo MDS can be further classified as refractory cytopenia (RC; previously known as refractory anemia or RA), RA with excess of blast (RAEB) and RAEB in transformation (RAEBt).

The European working party on myelodysplastic syndrome (EWOG-MDS) reported their retrospective results on 63 children with RC (Kardos et al., 2003). Over 40% of patients had hypocellular marrows. Almost 50% of children with monosomy 7 progressed to advanced MDS within 2 years from diagnosis. By contrast, patients with hypocellular RC with a normal karyotype, may experience a long stable course before progression to generalized marrow failure occurs. Therefore, in patients with monosomy 7, HSCT should be performed soon after the diagnosis has been established. This is also advised for patients with advanced MDS (RAEB or RAEBt), and for patients with hypercellular RC, or with other clonal aberrations. In some patients the differentiation between hypocellular RC with a normal karyotype and aplastic anemia may be difficult, and in such patients a "watch and wait" strategy may be considered with repeated bone marrow evaluation before a final decision on diagnosis and therapy is made.

After the introduction of the new WHO definition of acute myeloid leukemia, which lowered the threshold to diagnose AML from 30 to 20% blasts, there has been a debate whether RAEBt should be classified and treated as MDS or AML (VArdiman, 2002). One approach is to build in some observation time to assess progression, and to look for signs

indicative of AML, such as organomegaly or non-random chromosomal aberrations such as t(8;21) or inversion(16).

Another relevant question in this respect is whether patients with advanced MDS benefit from pre-HSCT chemotherapy or not. Current results indicate this is not the case, as outcome did not differ according to blast percentage <5%, 5-19% or >20% in directly transplanted patients (Stary, 2005).

In summary, patients diagnosed with advanced MDS should be treated with allogeneic-HSCT, which may even include less suitable donors such as mismatched or haploidentical donors if this is the only available choice for a particular patient.

2.4 Solid tumors

Neuroblastoma (stage IV beyond the age of 1 year, or high risk factors in lower stage) is still the only indication where the benefit of high-dose therapy with autologous HSCT has been shown by randomized trials (Ladenstein et al., 2008; Matthay et al., 2009).

Although to date the published results do not show an unequivocal benefit for consolidation with high-dose therapy, children and adolescents with solid tumors might undergo autologous HSCT after high-dose chemotherapy within clinical research trial, preferably as part of first –line treatment strategies in the following situations:

- Neuroblastoma (high risk, >CR1)
- Ewing's sarcoma (high risk or >CR1).
- Brain tumors: children with medulloblastoma and high-grade gliomas responsive to chemotherapy in an attempt to avoid or postpone radiotherapy.
- Soft tissue sarcoma: stage IV or in responding relapse.
- Germ cell tumors: after a relapse or with progressive disease.
- Wilm's tumor: relapse.
- Osteogenic sarcoma: the value of HSCT is not yet clear.

In general, allogeneic HSCT cannot be recommended in children with solid tumors. Allogeneic HSCT may be undertaken in the context of a clinical protocol in specialized centers.

2.5 Bone marrow failure (BMF)

BMF syndromes include a broad group of diseases of varying etiologies in which hematopoiesis is abnormal or completely arrested in one or more cell lines. BMF can be acquired aplastic anemia (AA) or can be congenital, as part of such syndromes as Fanconi anemia (FA), Diamond Blackfan anemia (DBA), and Shwachman Diamond syndrome (SDS). The estimated incidence of BMF is 2 per million in Europe, with higher rates in Asia, perhaps resulting from environmental factors.

2.5.1 Acquired severe aplastic anemia (AA)

HSCT using an HLA-matched related donor is the treatment of choice for severe acquired aplastic anemia, resulting in long-term survival rates of over 90% If an HLA-compatible

family donor is not available, most patients are treated with high-dose immunosuppression, using antithymocyte globulin (ATG) plus cyclosporine, with or without granulocyte colony-stimulating factor (G-CSF). Approximately 70-80% of patients respond to immunosuppression, although the actuarial 10-year survival rate is about 40%. Marrow transplantation from unrelated donors is reserved for those patients who do not respond to or who relapse after immunosuppressive therapy.

2.5.2 Inherited bone marrow failure syndromes (IBMFS)

IBMFS should be considered for all patients presenting with AA, regardless of the presence or absence of characteristic physical findings. IBMFS require specific approaches to management. Sensitive and specific diagnostic tests, including identification of mutations in specific genes, are available for many disorders.

2.5.2.1 Fanconi anemia (FA)

FA is the most common IBMFS and consists of a complex disorder of increased sensitivity to DNA damage characterized by congenital anomalies, progressive BMF, and high risk of MDS, malignant transformation to acute leukemia and solid tumors. Significantly, a large percentage of affected persons (25% to 40%) have no visible anomalies, and FA cannot be excluded without specific testing for mutagen sensitivity. BMF in FA typically presents between the ages of 5 and 10 years, with an actuarial risk of developing bone marrow failure of 50% to 90% by age 40 years (Kutler et al., 2003; Rosenberg, 2008). The median age of patients who develop AML is 14 years (Alter, 2003), and cumulative incidence of hematologic malignancy by age 40 years is 22% to 33% (Kutler et al., 2003; Rosenberg, 2008). Symptomatic transfusion, G-CSF, and androgens can be used to treat cytopenias; however, HSCT is the only current definitive therapy to restore normal hematopoiesis.

Commonly agreed-upon indications for HSCT in these patients include evidence of severe marrow failure as manifested by an ANC less then $1000 \times 10^9/L$ with or without G-CSF support, or hemoglobin of less than 8 g/dl or platelet count less than $50,000 \times 10^9/L$ or requirement of blood transfusion on regular basis. HSCT is also indicated for FA patients with evidence of progression to MDS or AML. Patients with FA who have an HLA-identical related donor, early HSCT is now the first-line treatment of choice for BMF, and preferably before transfusion dependence develops, to limit the risk of graft failure.

Preparative regimens for HSCT in FA patients are modified from standard approaches because of the chromosomal instability present in all FA cells, including nonhematopoietic tissues. In vitro studies have shown that FA cells are hypersensitive to DNA cross-linking agents, such as cytoxan (Berger, 1980). In addition, patients with FA are at increased risk of severe GVHD compared with patients with severe AA because of defective DNA repair mechanisms, leading to prolonged tissue damage after targeting by an alloreactive response (Guardiola et al., 2004).

Elaine Gluckman's group at St Louis, Paris investigated the use of reduced-dose cytoxan (20 to 40mg/kg) and reduced-dose thoracoabdominal irradiation or total body irradiation (TBI) (400-450 cGy) and reported a long-term survival of 58.5% after sibling donor transplantation, although with high incidences of aGVHD (55%) and cGVHD (70%). Later series modified the Gluckman regimen with the addition of ATG, resulting in less aGVHD

and cGVHD and improved survival (Ayas et al., 2001). A recent series of 35 FA patients undergoing matched-related HSCT using this regimen along with peri transplantation ATG reported an excellent 10-year actuarial survival of 89%, with aGVHD in 23% of cases and cGVHD in 12% of cases (Farzin et al., 2007).

These studies have used low dose radiation because patients with FA have an increased risk of posttransplantation malignancy, but what about avoiding radiation altogether? A recent retrospective review of experience with matched related HSCT in FA patients in Saudi Arabia by Ayas et al (Ayas et al., 2008) found significantly greater OS in patients receiving non radiation, low dose cytoxan and ATG regimens compared with those undergoing preparative regimens with cytoxan and additional thoracoabdominal radiation (72.5% vs 96.9%; p=0.013). The availability of fludarabine, a highly immunosuppressive nucleoside analog that is well tolerated by patients with FA, has allowed the elimination of radiation with good results. Tan et al in 2006, recently reported an actual OS of 82%, transplant related mortality of 9% and minimal GVHD in a cohort of 11 patients who underwent transplantation with low dose cytoxan, fludarabine and ATG with T cell-depleted bone marrow or umbilical cord cells.

HSCT from an unrelated donor for patients with FA remains a key treatment strategy. Historically, outcomes of alternative donor transplantation in FA have been discouraging, with high incidences of graft failure, aGVHD and cGVHD and organ toxicity related to preparative regimens. Many regimens have been looked at over the years for unrelated transplants including increasing the dose of radiation, adding ATG without significant improvement in overall survival. The advent of fludarabine based preparative regimens has resulted in considerable progress, improving engraftment without significant toxicity attributable to the drug. However, although fludarabine regimens have had some success in treating FA, concerns regarding reduced intensity conditioning (RIC) regimens persist; residual FA cells that survive the preparative regimen may present as AML as much as 10 years later (Ayas et al., 2001).Despite these data, (Chaudhury et al., 2008), in a study of 18 high-risk patients with transfusion dependent AA, MDS and AML receiving either related mismatched or unrelated matched or mismatched HSCT using fludarabine, TBI and cytoxan for preparative regimens with T-cell depleted stem cell sources, found 100% engraftment, OS 72.2% and DFS of 66.6% with a median follow up of 4.2 years, suggesting that a RIC preparative regimen might be sufficient to control malignancy in FA. Cord blood is an alternative stem cells source for patients with FA who lack an HLA-matched unrelated bone marrow donor, as umbilical cord blood transplant has decreased incidence of GVHD.

Despite the improved survival, identifying the ideal time for HSCT in FA patients requiring alternative donor transplantations remains challenging, given the still-significant peri transplantation mortality and the possibility of long lasting androgen response or survival with AA for a significant period without progression to MDS/AML. Referral and transplantation before exposure to large amounts of blood products or prolonged periods of severe neutropenia are likely to lead to the best outcomes.

2.5.2.2 Shwachman-diamond syndrome (SDS)

SDS is a rare autosomal recessive disorder characterized by exocrine pancreatic insufficiency, skeletal abnormalities and BMF with a predisposition to MDS and leukemia, especially AML. Although most patients with SDS have some hematologic abnormalities,

most of them do not require HSCT. In the largest reported series, 20% of cases developed pancytopenia and 6% progressed to MDS (Ginzberg et al., 1999).

HSCT is the only curative treatment for bone marrow dysfunction associated with SDS. However, the timing of HSCT remains a subject of controversy, and the apparent lack of genotype-phenotype correlation makes selection of patients for early preemptive HSCT difficult at present. In addition, SDS patients, like FA patients, have increased toxicity with intensive conditioning regimens. Overall, the available literature on HSCT in SDS patients is limited and consists mainly of case reports (Cesaro et al., 2001; Fleitz et al., 2002). Preliminary data indicates that HSCT with reduced intensity conditioning is feasible in patients with SDS and is associated with excellent donor cell engraftment and modest morbidity.

2.5.2.3 Dyskeratosis congenita (DS)

DC is a disorder of diverse inheritance with chromosomal instability related to a defect in telomere maintenance, characterized by a triad of reticulate skin pigmentation, mucosal leukoplakia and nail dystrophy, along with BMF. Between 80% and 90% of persons with DC will develop hematopoietic abnormalities by age 30 years, and BMF is the leading cause of early mortality in this population (Dokal, 2000). In addition, DC patients are at increased risk for MDS/AML and solid tumors, especially squamous cell carcinomas, as well as progressive pulmonary fibrosis (Dokal, 2000).

Allogeneic HSCT remains the only curative approach for marrow failure in patients with DC; however outcomes have been poor due to early and late complications. Initial attempts at HSCT in DC patients with myeloablative regimens had poor results, with significant morbidity and mortality, including increased incidences of chronic pulmonary and vascular complications, likely related to these patients underlying tendency to develop restrictive pulmonary disease. Non-myeloablative transplants using low-dose Cytoxan and fludarabine and ATG have produced successful engraftment and good short term outcomes, largely in case reports (de laFuente, 2007). Regardless of the potential reduction in toxicity associated with non-myeloablative regimens, preexisting conditions characteristic of DC (e.g. pulmonary disease) may ultimately limit the effectiveness of HSCT in DC patients.

2.5.2.4 Diamond-blackfan anemia (DBA)

DBA is a rare inherited form of pure red blood cell aplasia that presents early in infancy. Mutations in one of a number of ribosomal proteins have been identified in approximately 50% of DBA patients, implicating ribosomal biogenesis or function in the disorder. Clinically, DBA is associated with macrocytosis, reticulocytopenia, and normal marrow cellularity with erythroblastopenia. Characteristically, these patients have elevated fetal hemoglobin and erythrocyte adenosine deaminase activity, and up to 35% have an associated congenital anomaly, with craniofacial and thumb abnormalities the most common.

Corticosteroids remain the mainstay of initial therapy in DBA, with 80% response rate. Only 20% of patients achieve remission; 40% require continued therapy with steroids, which can have significant side effects, and another 40% remain transfusion and chelation dependent (Vlachos et al., 2008). Steroid-intolerant or transfusion-dependent patients may be considered for HSCT, which although curative for DBA, remains controversial, because most of these patients can achieve long-term survival with supportive therapy alone.

A series of 36 patients from the DBA registry who underwent HSCT (main indication transfusion dependence) yielded 5-year survival rates of 72.7% in matched sibling donor recipients and 19% in alternative donor recipients (p=0.01) (Lipton et al., 2006). Similar results were reported in an international bone marrow transplant registry series of 61 patients with DBA undergoing HSCT with conventional cytoxan containing preparative regimens; 3-year survival was 76% after sibling donor transplantation compared with 39% after alternative donor transplantation (Roy et al., 2005). In both studies, the alternative donor recipients were more likely to have received a TBI-containing regimen or to have a longer time from diagnosis to transplantation, suggesting that TBI should be avoided. In addition, patients with DBA have an increased risk of malignancy compared to the general population, another reason why TBI-containing regimens should be avoided in this population. There also are encouraging case reports of successful HSCT in DBA with RIC fludarabine containing preparative regimens; however, the data are scanty and reflect short follow-up times; further study is needed in this area (Berndt, 2004; Ostronoff, 2004).

2.5.2.5 Congenital Amegakaryocytic Thrombocytopenia (CAMT)

CAMT is a rare autosomal recessive disorder caused by mutations in the thrombopoietin receptor. It is usually diagnosed early in childhood, presenting with isolated nonimmune thrombocytopenia with decreased marrow megakaryocytes. Approximately 50% of CAMT patients develop marrow aplasia, and some develop MDS or leukemia.

Although transient responses to steroids, cyclosporine and growth factors in CAMT have been documented, HSCT remains the only curative treatment. Good short-term survival has been reported after matched related donor HSCT in small case series. Reports of unrelated donor HSCT are largely case reports and describe significant engraftment challenges.

2.6 Immunodeficiencies

Primary cellular immunodeficiencies are a group of inherited disorders characterized by severe impairment of the innate or adaptive immune systems, which generally leads to early death from infectious complications. These disorders can be further categorized by the cell lineage primarily affected (table 6). Supportive care can extend the life span of patients affected by these diseases, definitive cure is generally only achieved by allogeneic hematopoietic stem cell transplantation, though recent advances in gene therapy hold significant promise that this may soon be a viable alternative. Allogeneic HSCT is indicated for severe primary immunodeficiencies from both HLA-identical and alternative donors.

Absent T- and B- lymphocyte function	Defective T and B lymphocytes	Dysfunctional T lymphocytes with predisposition to HLH	Absent or dysfunctional granulocytes
SCID	Wiskott–Aldrich syndrome	Familial HLH (defects in *perforin*, *MUNC*, etc.)	Severe congenital neutropenia
	HIGM1	Chediak–Higashi syndrome	Leukocyte adhesion disorder
		Griscelli syndrome	Chronic granulomatous disease
		XLP	

Abbreviations: HIGM1 = hyper IgM syndrome (CD40 ligand deficiency); HLH = hemophagocytic lymphohistiocytosis; XLP = X-linked lymphoproliferative disease.

Table 6. Primary Immunodeficiencies Potentially Treated with HSCT.

2.6.1 Severe combined immunodeficiency (SCID)

SCID is a rare disorder caused by a group of genetic disorders with a shared phenotype of deficient T and B lymphocyte infunction (with or without abnormal natural killer (NK) cell development) that leads to early death from recurrent infections in affected children (table 7). Except for those patients with SCID due to deficiency of adenosine deaminase (ADA), for which replacement enzyme exists, the only curative therapy for SCIS is allogeneic HSCT. However, early results with gene insertion into autologous hematopoietic stem cells for children with x-linked SCID and ADA deficiency (Cavazzana-Calco, 2007) suggest that eventually this will become a more common form of curative treatment for many primary immunodeficiency diseases.

Name	Defect	Phenotype	Special
X-linked	Common γ chain	T-B + NK −	
JAK3 deficiency	Janus kinase 3	T-B + NK −	
Rag 1 or 2	Recombinase-activating proteins 1 or 2	T-B−NK +	Frequently associated with Omenn's syndrome: autoreactive GVHD
Artemis deficiency	Artemis (also known as DCLRE1C)	T-B−NK +	Athabascan-speaking Native Americans, radiosensitive
Ligase 4 deficiency	Ligase 4	T-B−NK +	Radiosensitive
IL-7Rα deficiency	IL-7 receptorα	T-B + NK +	
CD45 deficiency	CD45	T-B + NK +	
CD3δ deficiency	CD3δ subunit	T-B + NK +	
CD3ε deficiency	CD3ε subunit	T-B + NK +	
CD3ς deficiency	CD3ς subunit	T-B + NK +	
Cartilage hair hypoplasia	Endoribonuclease	T-B + NK +	Dwarfism, hypoplastic hair Finnish, Amish
p56lck deficiency	p56lck Protein tyrosine kinase	T-B + NK +	
ADA deficiency	Adenosine deaminase	T-B−NK −	
PNP deficiency	Purine nucleoside phosphorylase	T-B−NK −	Neurologic dysfunction, ataxia
Reticular dysgenesis	Unknown	T-B−NK −	Impaired myeloid and erythroid development, sensorineural deafness
ZAP70 deficiency	ς-chain-associated protein kinase	CD4 +, CD8− B +, NK +	
Bare lymphocyte Syndrome type II	HLA class II	CD4−(mild), CD8 + B +, NK +	North African
SCID with bowel atresia	Unknown	CD4 +, CD8 +, B + NK +	

Abbreviations: ADA = adenosine deaminase; DCLREIC = DNA cross-link repair enzyme 1C; HLA = human leukocyte antigen.

Table 7. Genetic Sub-Types of Severe Combined Immunodeficiency.

HSCT should be done as soon as the diagnosis is confirmed because these patients are at risk of developing a life-threatening infection, particularly pulmonary infections. For all stem cell sources, successful outcomes are more likely to be achieved when the patient is still very young, preferably less than 6 months of age.(Buckley et al., 1999), demonstrated that infants transplanted less than 3.5 months of age had a 95% overall survival compared to only 76% overall survival in older children. The preferred choice of stem cell donor for a patient with SCID is an HLA-identical sibling, in which the overall survival now exceeds 90%, if the transplant is performed promptly. In patients without a matched sibling, the choice is whether to use an immediately available T cell depleted haplocompatible family member or to perform a search for an HLA matched unrelated donor or cord blood unit. Table 8 lists the reports on transplantation with different stem cell sources.

2.6.2 Wiskott-Aldrich syndrome (WAS)

WAS is characterized by a trial of thrombocytopenia with small platelets, eczema and recurrent infections. The T cell immunodeficiency predisposes to the development of autoimmune phenomena and lymphoma. Affected males rarely survive past the second

decade of life. The only curative strategy is allogeneic HSCT. The international bone marrow registry and national marrow donor program demonstrated in 170 patients that while the 5-year OS of patients transplanted from HLA-identical siblings was 87%, the results for unrelated HSCT were significantly related to the age at transplant (Filipovich et al., 2001). Unrelated donors less than 5 years of age had an 85% 5-year OS, while all 15 patients greater than 5 years of age died (Filipovich et al., 2001). Haploidentical related transplants have been less successful with an OS of 45-52%.

	Year	Reference	MRD	Haplo	Haplo	MUD	MUD	Cord
Conditioning			None	None	MA	MA	RI	MA
Dror et al.	1993	*	—	67% (12)	50% (12)	—	—	—
Buckley et al.	1999	?	100% (12)	78% (77)	—	—	—	66% (3)
Bertrand et al.	1999	*	—	46% (50)	54% (129)	—	—	—
Dalal et al.	2000	15	—	—	—	67% (9)	—	—
Knusen and Wall	2000	16	—	—	—	—	—	88% (8)
Antoine et al.	2003	*	81% (104)	—	—	63% (28)	—	—
Rao et al.	2005	8	—	—	—	71% (7)	83% (6)	—
Bhattacharya et al.	2005	16	—	—	—	—	—	80% (10)*
Grunebaum et al.	2006	14	92% (13)	—	53% (40)	81% (41)	—	—

Stem cell source: MRD (matched related donor) vs haplo (haplocompatible family donor) vs MUD (matched unrelated donor) vs Cord (unrelated cord blood stem cells). Conditioning: none vs MA (myeloablative) vs RI (reduced intensity). Percentage indicates overall survival (absolute number of patients). *Some patients received no conditioning.

Table 8. Survival Following HSCT For SCID Based on Stem Cell Source and Conditioning Regimen.

2.6.3 Familial hemophagocytic lymphohistiocytosis (HLH)

Familial HLH is characterized by episodes of fever, hepatosplenomegaly and cytopenias. An autosomal recessive defect in one of the several genes including those encoding perforin or Munc 13, causes reduced NK and T cell cytotoxicity. This leads to a widespread accumulation of lymphocytes and mature macrophages with hypercytokinemia. Familial HLH is invariably fatal. The only curative strategy for treatment of familial HLH is allogeneic HSCT. A report from a multicenter prospective trial, HLH-94, demonstrated a 62% 3-year EFS in 65 children undergoing allogeneic HSCT with a variety of stem cell sources (Henter et al., 2002).

2.6.4 Chronic granulomatous disease (CGD)

CGD is characterized by recurrent pyogenic infections in patients with normal neutrophil numbers. A defect in one of the four genes encoding subunits of the nicotinamide adenine dinucleotide phosphate-oxidase complex leads to insufficient production of free protons from which to make hydrogen peroxide. With good supportive care, including therapy with interferon gamma, affected individuals can live up to the fourth decade of life, but suffer early mortality from recurrent pulmonary infections.

Allogeneic HSCT is the only curative strategy. A report from the European group for Blood and Marrow Transplantation demonstrated in 23 patients that myeloablative conditioning prior to matched sibling HSCT can be safely performed (85%OS), especially if the patient were free of infection at the time of HSCT (100% OS) (Seger et al., 2002). Given the current success rates, some favor transplantation in all patients with CGD who have an appropriate donor at the earliest opportunity.

Recent data, (Kuhn's et al., 2010) showed that patients with very low superoxide production had worse long-term survival than those with higher levels of NADPH oxidase activity

suggesting that these patients should be considered appropriate candidates for early HSCT, particularly if a sibling matched donor is available. An increased alkaline phosphatase level, a history of liver abscesses, and a decrease in platelet count reflecting portal hypertension are adverse prognostic indicators (Feld et al., 2008). These patients might also be considered for early transplantation. Even with improved survival and longevity caused by better infection and inflammation management, complications and their consequences can accumulate over time. However, HSCT is probably better before infections and inflammatory damage accumulates. Transplantation has aloes reversed some of the inflammatory and autoimmune complications associated with CGD and might prevent their development (Seger et al., 2002). Allogeneic HSCT has improved dramatically over the last decade because of improved conditioning regimens and GVHD prophylaxis, high-resolution sequence-based matching and improved pre transplantation, peri transplantation and post transplantation management and as a result it has become a successful and sensible option for many patients with CGD.

2.7 Inherited metabolic diseases (IMD)

IMD is a diverse group of diseases arising from genetic defects in lysosomal enzymes or peroxisomal function. The lysosome is an intracellular sorting, recycling and digestion of organic molecules. Loss of functional activity of lysosomal enzymes results in accumulation of substrates, such as glycoprotein or mucopolysaccharides (MPS). The clinical manifestations vary depending on the specific enzymatic deficiency, level of residual activity, and site of substrate accumulation.

Allogeneic HSCT can prolong life and improve its quality in patients with IMD. HSCT offers a permanent source of enzyme replacement therapy and also might mediate nonhematopoietic cell regeneration or repair. The likely processes responsible for the effectiveness of HSCT for IMD includes cytoreduction to ablate myeloid and immune elements, engraftment of donor-derived hematopoietic and immune system, donor leukocytes production of enzyme, distribution of enzyme through blood circulation, migration of cells to brain, cross blood-brain barrier, many develop microglia, replacement of enzyme in the brain by cross-correction and nonhematopoietic cell engraftment (Prasad and Kurtzberg, 2008).HSCT has been performed in almost 20 of the 40 known lysosomal storage disorders and peroxisomal storage disorders. However, the majority of transplant experience to date is in patients with MPS I (Hurler Syndrome), other MPS syndromes (MPSII, MPSIII, A & B, MPSVI), adrenal leukodystrophy (ALD), metachromic leukodystrophy (MLD), and globoid leukodystrophy (Krabbe disease), accounting for more than 80% of the cases. Table 9 identifies the IMD for which allogeneic HSCT is currently indicated or under investigation. The response to HSCT varies from disease to disease, within patients with same disease, and within different organ systems in the same patient.

2.7.1 Hurler syndrome (MPS IH)

MPS IH, the most sever phenotype of alpha-l-iduronidase deficiency, is an autosomal recessive disorder characterized by progressive accumulation of stored glycosaminoglycans (GAGs). Hurler and other phenotypes of MPS I are a broad continuous clinical spectrum. Accumulation of GAGs results in progressive, multisystem dysfunction that includes

psychomotor retardation, severe skeletal malformations, life-threatening cardiopulmonary complications, and early death.

Disorder	Enzyme/Protein	HSCT Indication	Comments
Mucopolysaccharidoses			
Hurler (MPS IH)	α-ʟ-Iduronidase	Standard therapy	
Hurler/Scheie (MPS IH/S)	α-ʟ-Iduronidase	Optional	ERT first-line therapy
Scheie (MPS IS)	α-ʟ-Iduronidase	Optional	ERT first-line therapy
Hunter: severe (MPS IIA)	Iduronate-2-sulfatase	Investigational	Only early or asymptomatic
Hunter: attenuated (MPS IIB)	Iduronate-2-sulfatase	Investigational	Only early or asymptomatic
Sanfilippo (MPS IIIA)	Heparan-N-sulfatase	Investigational	Only early or asymptomatic
Sanfilippo (MPS IIIB)	N-Acetylglucosaminidase	Investigational	Only early or asymptomatic
Sanfilippo (MPS IIIC)	AcetylCoA:N-acetyltransferase	Investigational	Only early or asymptomatic
Sanfilippo (MPS IIID)	N-Acetylglucosamine 6-sulfatase	Investigational	Only early or asymptomatic
Maroteaux-Lamy (MPS VI)	Arylsulfatase B	Optional	ERT first-line therapy
Sly (MPS VII)	β-Glucuronidase	Optional	
Leukodystrophies			
X-ALD, cerebral	ALD protein	Standard therapy	Not for advanced disease
MLD: early onset	ARSA	Unknown	Only early or asymptomatic
MLD: late onset	ARSA	Standard therapy	
GLD: early onset	GALC	Standard therapy	Neonate, screening diagnosis, or second case in known family; not for advanced disease
GLD: late onset	GALC	Optional	
Glycoprotein metabolic and miscellaneous disorders			
Fucosidosis	Fucosidase	Optional	
α-Mannosidosis	α-Mannosidase	Optional	
Aspartylglucosaminuria	Aspartylglucosaminidase	Optional	
Farber	Ceraminidase	Optional	
Tay-Sachs: early onset	Hexosaminidase A	Unknown	Neonate, screening diagnosis, or second case in known family
Tay-Sachs: juvenile	Hexosaminidase A	Unknown	
Sandhoff: early onset	Hexosaminidase A & B	Unknown	Neonate, screening diagnosis, or second case in known family
Sandhoff: juvenile	Hexosaminidase A & B	Unknown	
Gaucher 1 (nonneuronopathic)	Glucocerebrosidase	Optional	ERT first-line therapy
Gaucher 2 (acute neuronopathic)	Glucocerebrosidase	Unknown	
Gaucher 3 (subacute neuronopathic)	Glucocerebrosidase	Unknown	Limited benefit of ERT
Gaucher 3 (Norrbottnian)	Glucocerebrosidase	Optional	
Pompe	Glucosidase	Investigational	ERT available
Niemann-Pick: type A	Acid sphingomyelinase	Unknown	
Niemann-Pick: type B	Acid sphingomyelinase	Unknown	ERT in clinical trial
Niemann-Pick: type C	Cholesterol trafficking	Optional for C-2	
Mucolipidosis: type II (I-cell)	N-Acetylglucosamine-1-phosphotransferase	Investigational	Only early or asymptomatic
Wolman syndrome	Acid lipase	Optional	May be viewed as standard
MSD	Sulfatases	Investigational	

Table does not include diseases where HSCT is not indicated. Standard therapy: HSCT applied routinely. Considerable published research evidence from registries and institutions shows efficacy. Delayed diagnosis or advanced disease may preclude transplant for individual patients. Optional: HSCT is effective but other therapy is increasingly considered first choice. Or, insufficient published evidence for HSCT to be considered standard. Investigational: possible a priori reason for HSCT. Further published evidence needed to support the use of HSCT in clinical practice. Unknown: no published evidence that HSCT is beneficial.

Table 9. IMD for which HSCT may be indicated

Data from the CIBMTR and EBMT indicate that more than 500 allogeneic HSCTs have been performed worldwide for children with MPS IH since 1980, making it the most commonly transplanted IMD. HSCT is effective, resulting in increased life expectancy and improvement of clinical parameters if performed early in the disease course before the onset of irreversible damage. Donor engraftment after HSCT has resulted in improvement of the following clinical symptoms: rapid reduction of obstructive airway symptoms, and hepatomegaly; improvement in cardiovascular function as well as hearing, vision and linear growth; finally hydrocephalus is either prevented or stabilized. In addition, cerebral damage already present before HSCT seems to be irreversible, but HSCT is able to prevent progressive psychomotor deterioration and improve cognitive function (Peters, 1998; Vellodi et al., 1997).

A matched normal sibling is the preferred HSCT donor. In the past decade an unrelated cord blood (CB) has been used with increasing frequency in patients without a sibling donor. CB offers several potential advantages compared with bone marrow or peripheral blood for HSCT, including better availability, greater tolerance for HLA mismatches, lower incidence and severity of GVHD and reduced likelihood of transmitting viral infections (Staba et al., 2004; Prasad et al., 2008). The use of CB for children with MPS IH has been associated with high rates of chimerism, engraftment and overall survival (Staba et al., 2004; Prasad et al., 2008). Similar results are noted for CB in other selected IMD (Escolar et al., 2005). As a result of this data, the EBMT developed transplantation guidelines for patients with MPS IH in 2005. These guidelines are widely used today and include a standardized busulfan/cytoxan (BU/CY) conditioning regimen, an enzymatically normal matched sibling bone marrow donor if available, and if not, cord blood as the preferred graft source. A recent EUROCORD- Duke university MPS IH collaborative study showed that early transplant (i.e., within 4.6 months from diagnosis) with CB and BU/Cy conditioning was associated with improved engraftment and overall survival. Furthermore, 94% of engrafted survivors achieved full donor chimerism. (Boelens et al., 2007).

Despite the overall success from HSCT, some disease manifestations persists or can even progress after HSCT, and this includes the musculoskeletal disorders secondary to the IMD that does not resolve and often requires orthopedic surgical intervention. In addition, neurocognitive dysfunction and corneal clouding that developed before HSCT may be irreversible. The outcome of HSCT for children with MPS IH is promising, yet variable from child to child. The variability is presumably caused by factors such as genotype, age and clinical status before HSCT, donor enzyme activity level, donor chimerism (mixed or full) stem cell source (CB, BM,PB) and resultant enzyme activity level in the recipient (Aldenhoven, 2008). An international long-term follow up study involving Europe and North America is underway to evaluate the influence of these various factors. Overall progress has been made. HSCT for children with MPS IH has become a safer procedure, with recent survival rates exceeding 90%.

2.7.2 Other mucopolysaccharidosis syndromes

Compared with MPS IH, experience with HSCT for treatment of other MPS disorders is limited. Small numbers and lack of detailed functional outcome data hamper the development of specific therapy guidelines. Conceptually, the basis for the effectiveness of HSCT in these children is the same as those with MPS IH. However, the kinetics of cellular migration, differentiation, distribution, and effective enzyme delivery may differ. Also, there is wide clinical variability within and across specific MPS diseases. As with HSCT for other IMD, important factors in the outcome may be timing of transplant, graft source, and the underlying severity of the phenotype in a given child. To date, most of the published experience is in recipients of BMT (Guffon et al., 2009). Recently, survival has been reported in small cohorts undergoing CBT, but their functional outcomes are not yet published.

The role of HSCT in MPS II remains controversial because of lack of convincing evidence of neurocognitive benefit. The status of HSCT for Sanfilippo Syndrome (MPS III) is similar to that of MPS II with inadequate data and inability to make specific recommendations about timing of transplant, graft source, and potential neurological benefit. Eleven long-term survivors of BMT have been reported, but all showed declined in neurocognitive function

(Gungor,1995; Vellodi et al., 1992). On the other hand, the results of HSCT for Maroteaux-Lamy Syndrome (MPS VI) have been promising. MPS VI has multiple clinical phenotypes, but generally patients live into the second to fourth decade. HSCT in 4 patients with MPS VI lead to improvement in cardiopulmonary function, facial features, and quality of life (Herskhovitz et al., 1999). HSCT can be considered a therapeutic option for patients with MPS VI that are intolerant or fail ERT.

2.7.3 Adrenal leukodystrophy (ALD)

X-ALD is a peroxisomal disorder involving defective beta-oxidation of very long chain fatty acids (VLCFA). The affected gene in X-ALD is ABCD1 and the peroxisomal membrane protein for which it codes is ALDP. More than 500 mutations in the gene are described, but there is no relationship between the nature of the mutation and the clinical presentation of illness. X-ALD has a variable clinical presentation. Patients can be asymptomatic or present with adrenal insufficiency and/or non inflammatory axonopathy (AMN) and/or cerebral disease. The clinical course is so variable with some individuals never developing symptoms so therefore, HSCT can not be recommended based on the presence or absence of the genetic mutation. HSCT is indicated only in those patients with clear evidence of early cerebral inflammatory disease as determined by a gadolinium enhanced MRI. (Peters, 2003). Cerebral disease may manifest itself during childhood or adolescence. Approximately 40% of genetically affected boys develop childhood cerebral X-ALD. Many of the remainder develops AMN. Cerebral disease is usually progressive, although clinical stabilization without HSCT can occur. HSCT is not currently indicated for asymptomatic individuals as prophylaxis. In view of the natural history of the disease such a practice would mean that some boys would undergo HSCT (with its short-term mortality and long-term morbidity risks) who might otherwise have been healthy. Nor is indicated for those individuals with advanced cerebral disease because HSCT does not reverse and may even worsen, established disease.

In this disease, judicious timing of the transplant is paramount. Asymptomatic boys should be regularly screened for signs of inflammatory brain disease, a potential donor identified, and HSCT rapidly performed if and when such symptoms appear. The presence of brain MRI abnormalities and the presence or absence of enhancement with gadolinium has been shown to be of prognostic value. A 34-point MRI scoring system specific for X-ALD that was designed by Loes and colleagues (Loes et al., 1994; Loes et al., 2003) is now used worldwide for patient evaluation and treatment decisions. An MRI severity score as low as 1 with gadolinium enhancement in a young boy is highly predictive of subsequent progressive demyelination and is an indication for transplant. However, the identification of an HSCT donor for asymptomatic boys should not await MRI anomalies, but should done immediately after diagnosis to prevent delays if a follow up MRI indicates disease progression.

Review of the literature supports that most boys that have been transplanted from the best available donor have received full intensity chemotherapy-only preparative regimen (Peters, 2004); most unrelated donors have been adult bone marrow donors, but some CB donors have been used (Beam, 2007); donor-derived engraftment rates seem higher than seen in patients transplanted for MPS IH syndrome (86% of 93 evaluable patients at a median follow-up of 11 months; 93% of related donor transplants; 80% of unrelated donor

transplant) (Peters,1998,2004); outcome is affected by disease status, donor source and HLA matching (Peters, 2004). The most common causes of death are progressive cerebral X-ALD disease and GVHD. TRM is 10% in related donors and 18% in unrelated donors. Five-year survival rates for recipients of related donor and unrelated donor transplants have been reported at 64% and 53%, respectively (Peters, 2004); and finally, survival is clearly affected by disease status at time of transplant as assessed by the number of neurologic deficits and MRI severity score. In those with 0 or 1 neurologic deficit and MRI score of less than 9, the 5-year survival was 92% compare to 45% in all other patients (Peters, 2004).

2.7.4 Globoid leukodystrophy (GLD)

GLD or Krabbe disease is an autosomal recessive lysosomal storage disorder caused by deficiency of galactocerebrosidase (GALC), an enzyme responsible for degrading beta-galactocerebroside, a major component of myelin sheath. GALC deficiency causes defective and decreased myelination and inflammation in the CNS and peripheral nervous systems from catabolic derivatives of beta-galactocerebroside such as psychosine. These changes lead to progressive deterioration in neurologic and cognitive function, resulting in spasticity, mental deterioration, blindness, deafness, seizures and early death. In the most severe "early onset or infantile" form, children develop symptoms before 6 months of age and usually die by age 2. In the "late onset" form, symptoms appear in early to late childhood, but only a few children survive into teenage years.

HSCT is the only available therapy with potential to improve neurocognitive function, increase survival and alter the natural history of the disease. Krivit and colleagues (Krivit et al., 1998) described the use of allogeneic HSCT to treat 5 patients with GLD (4 received HLA-sibling HSCT & 1 unrelated cord). Two children with late onset GLD had substantial neurologic disability and they had resolution of their symptoms after transplant. Cognition, language and memory continued to develop normally in 3 children with late-onset disease. Most children had improvement in MRI, CSF protein levels, and all had normalization of enzyme activity. These findings support the use of allogeneic HSCT for children with GLD. If a matched related donor is not available, unrelated cord blood has also been shown to be beneficial (Escolar et al., 2005).

2.7.5 Metachromatic leukodystrophy (MLD)

MLD is an autosomal recessive lysosomal disorder arising from deficiency of arylsulfatase A (ARSA) enzyme activity and characterized by increased urinary sulfatides. The clinical phenotype is a broad continuous spectrum ranging from early-infantile MLD to adult-onset forms. Clinical symptoms vary depending on timing of presentation (infantile, juvenile or adult form), but all include abnormal cognitive skills, behavioral abnormalities with adults having mental regression and psychiatric symptoms, progressive spastic disease and increased CSF protein.

The first BMT for MLD was performed more than 20 years ago. According to the EBMT and CIBMTR registries, more than 100 transplants have since been performed for this disorder. Despite this number, the lack of graft-outcome and long-term follow up studies makes it

difficult to draw firm conclusions regarding the efficacy of HSCT in MLD. In addition, data suggest that outcomes are less promising than those for MPS IH. It is not clear if MLD patients, or which phenotypes, might benefit from HSCT. For presymptomatic juvenile and adult onset patients there is positive evidence. Improved transplantation techniques and the prompt availability of CB grafts may positively influence long-term outcomes. An international registry would facilitate comparative evaluation of therapeutic options, leading to improved guidelines.

3. Expanding Indications for transplant

HSCT has been explored in a number of malignant and nonmalignant diseases. Currently, research is rapidly expanding in areas not historically considered for HSCT. Also, as morbidity and mortality decrease, HSCT is being reconsidered for many diseases in which HSCT was previously considered and rejected. Several potential indications are reported in this section.

3.1 Beta-thalassemia

Thalassemias result from mutations of the globin genes that cause reduced or absent hemoglobin production, reducing oxygen delivery. To treat the anemia and restore oxygen delivery to tissues, chronic lifelong transfusions are required in those who have thalassemia major. However, this promotes progressive iron overload and organ damage. The only definitive cure for thalassemia is to correct the genetic defect by HSCT. Transplantation is recommended early, if an allogeneic healthy related sibling donor or a related CB is available. Several studies have suggested that umbilical cord blood transplant (UCBT) recipients benefit from a lower risk of GVHD (Gluckman, 1997; Wagner, 1995) and a recent analysis comparing 113 children who received a UCBT from a compatible sibling with 2052 HLA-identical sibling marrow transplant recipients showed that children receiving UCB experienced a significantly reduced risk of developing aGVHD and cGVHD (Rocha, 2000).

Prior to transplant, the patient should be assigned to 1 of 3 Pesaro risk class to assess risk factors for BMT. This classification is based upon clinical features of thalassemia that include: (1) adherence to a program of regular iron chelation therapy, (2) the presence or absence of hepatomegaly and (3) the presence or absence of portal fibrosis observed by liver biopsy. The conditioning regimen is uniform for classes 1 and 2 patients, but is modified for those who have class 3 features due to an increased risk of transplant-related mortality (Lucarelli, 1990). As a result of this risk classification and the development of new conditioning regimens, the outcome of thalassemia patients have improved with thalassemia-free survival and EFS over 70% reported worldwide. When stratifying patients, initially those with Pesaro Class 1 characteristics < 17 years had a superior thalassemia-free survival; however, recent updates show that outcomes are very similar across all three risk categories after employing risk-based conditioning regimens (Bhatia, 2008). Unrelated donor transplants are also used in selected patients (Bhatia, 2008). Following transplant, iron overload may still be a problem; consequently, chelation or phlebotomy may still be necessary.

3.2 Sickle cell disease (SCD)

SCD contrasts with thalassemia major by its variable course of clinical severity. Its typical clinical manifestation include anemia, severe painful crisis, acute chest syndrome, splenic

sequestration, stroke (clinically overt and silent), chronic pulmonary and renal dysfunction, growth retardation, neuropsychological deficits and premature death. Historically, the mainstays of treatment are both preventive and supportive. The three major therapeutic options available for children affected with SCD are: chronic blood transfusion, hydroxyurea and HSCT. Of these options, only HSCT affords patients the possibility of cure. The use of transplantation for the treatment of patients with SCD has been considered for many years. However, because of the morbidity and mortality of HSCT, it was considered too risky. Recently, due to advances in supportive care and immunosuppressive therapy, transplant is again being considered for SCD. The preliminary experience of HSCT for beta-thalassemia major has in part provided the rationale for extending this treatment to sickle cell anemia. Walter et al (Walter et al., 1996) used selection criteria similar to that applied to patients with beta thalassemia major and chose patients with debilitating clinical events, including stroke, recurrent acute chest syndrome and recurrent painful vaso-occlusive crises, but selected children rather than adults and before the development of permanent end organ damage. These recommendations are associated with significant morbidity and early mortality among patients with SCD and are the criteria upon which most early studies using HSCT are based.

Three major clinical series account for most of the experience of HSCT for SCD (Bernaudin et al, 2007; Walters et al, 2000; Vermylen et al, 1998). In all three series, the majority of patients received HLA-identical sibling donor allograft and all patients received the same conditioning regimen (busulfan 14-16mg/kg with cytoxan 200) and GVHD prophylaxis (ATG, cyclosporine and methotrexate). The results of these three studies were very similar. OS was 92-94% and EFS was 82-86% with a median follow-up range of 0.9-17.9 years. TRM from all three series was also similar and was approximately 7% with infections as the chief cause. Similarly, the incidence of aGVHD > grade II was approximately 15-20%. The rate of cGVHD was 20% in Vermylen et al study compared to 12 and 13.5% in the Walters et al and Bernaudin et al reports, respectively. While HSCT is curative in patients with SCD, only 14-18% of patients have a matched family donor. The use of unrelated donors in HSCT for SCD is under development. There are several limitations which restrict the uniform utilization of allogeneic adult donors that include donor availability, and the high risk of severe aGVHD. The use of unrelated cord blood transplantation is also being considered and recent studies have shown promising results, although g raft rejection and aGVHD still remain issues. In addition, efforts to expand the application of HSCT for SCD have been restricted not only by lacking suitable donors, but also by the risk of significant toxicity from the myeloablative conditioning regimen. With the advent of lower intensity conditioning regimens which rely on less myeloablation and more immunosuppression, many of the long-term effects, such as growth and endocrine dysfunction observed after myeloablative conditioning regimens, may be ameliorated.

3.3 Autoimmune disease

Autoimmune diseases are often controlled with treatments that act on the immune system. However, these therapies are usually not curative. Recently many autoimmune diseases have been treated with HSCT. The goal of autologous HSCT is to reset the immune system. Studies on thymic lymphocytes after auto HSCT have shown that, after a

burst sustained by pre transplant memory cells, the organ is repopulated by likely harvest-derived naïve T cells, and also the T-lymphocyte repertoire may significantly differ before and after autografting, thus suggesting the possibility of achieving an immune resetting through autologous HSCT (Isaacs, 2004; Sun, 2004). Allogeneic probably results in the highest potential for cure. However, there is higher morbidity and mortality caused by GVHD. Marmont summarize several allogeneic transplant cases in which the patient achieved full post transplant donor chimerism but their autoimmune disease still relapsed. A European database, the International Autoimmune Disease Stem Cell Project Database, was established in 1996. The database contains 600 patients, most treated with autologous HSCT; 15% of the patients registered are children. Some of the autoimmune diseases in children that were treated with HSCT are juvenile idiopathic arthritis, immune cytopenias, systemic sclerosis, systemic lupus and Crohn's disease (Rabusin, 2008).

3.4 Other non-malignant disease

3.4.1 Autosomal recessive osteopetrosis (ARO)

ARO is a rare genetic bone disease in which a deficit in bone resorption by osteoclasts leads to increased bone density and secondary defects. The disease is often lethal early in life unless treated with HSCT. However, recently the dissection of the molecular bases of the disease has shown that ARO is genetically heterogeneous and has revealed the presence of subsets of patients which do not benefit from HSCT, highlighting the importance of molecular diagnosing ARO to identify and establish the proper therapies for better prognosis (Villa, 2008). EBMT conducted a retrospective analysis of 122 children who had received an allogeneic HSCT for ARO between 1980 and 2001. The actuarial probabilities of 5 years disease free survival were 73% for recipients of a genotype HLA-identical HSCT (n=40), 43% for recipients of a phenotype HLA-identical or one HLA antigen mismatch graft from a related donor (n=21), 40% for recipients of a graft from a matched unrelated donor (n=20) and 24% for patients who received a graft from an HLA-haplotype-mismatch related donor (n=41). Causes of death after HSCT were graft failure and early-TRM complications. Conservation of vision was better in children transplanted before the age of 3 months (Driessen, 2003). HSCT is the only curative treatment for ARO and should be offered as early as possible.

3.4.2 Congenital erythropoietic porphyria (CEP)

CEP is a rare autosomal recessive disorder of porphyrin metabolism in which the genetic defect is the deficiency of uroporphyrinogen III cosynthase (UIIIC). Deficiency of this enzyme results in an accumulation of high amounts of uroporphyrin I in all tissues leading to hemolytic anemia, splenomegaly, erythrodontia, bone fragility, exquisite photosensitivity and mutilating skin lesions. The vital prognosis is very bad and until now, no treatment seems to be efficient. Bone marrow transplantation seems to be able to correct the enzymatic deficit that causes the disease because it is located in the bone marrow. A few cases of patients have been reported to be cured of the disease with stem cell transplantation (Shaw, 2001). HSCT should be strongly considered because this is currently the only known curative therapy.

3.4.3 Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome

IPEX syndrome is a rare, fatal autoimmune disorder caused by mutations in the forkhead box protein 3 (FOXP3) genes leading to the disruption of signaling pathways involved in regulatory T-Lymphocyte function. Patients with IPEX syndrome often present in early infancy and without therapeutic intervention, affected male patients usually die within the first or second year of life. These patients require supportive therapy including parental nutrition, insulin, antibiotics and blood transfusions. Immunosuppressive therapy has been used with variable improvement in symptoms. Correction of the dysregulated immune system can be achieved by allogeneic HSCT using a suitable donor. Although, HSCT is the only viable option for long-term survival, patients are usually very ill to tolerate traditional myeloablative conditioning regimens. Recent studies reported the successful outcome of HSCT using a low-intensity, nonmyeloablative conditioning regimen in 2 patients with IPEX syndrome and significant pre transplant risk factors (Burroughs, 2010; Rao, 2007).

3.4.4 Epidermolysis bullosa (EM)

EB is a group of blistering skin disorders resulting from mutations in genes encoding protein components of the cutaneous basement membrane zone. HSCT has been shown to ameliorate the deficiency of the skin-specific structural protein in children with EB (Fujita, 2010; Tolar, 2011).

4. Conclusion

The indications for HSCT are continually changing and expanding rapidly beyond the traditional use as a treatment for malignant and nonmalignant diseases. The inclusion of cord blood as a source of stem cells and the availability of reduce intensity regimens has allowed us to expand the indications for HSCT to patients who otherwise would not meet accepted criteria for conventional HSCT. The field of HSCT is continually growing and a great deal of additional research is needed to continue to improve our outcomes. This is an exciting time in HSCT with many new avenues becoming available for patients.

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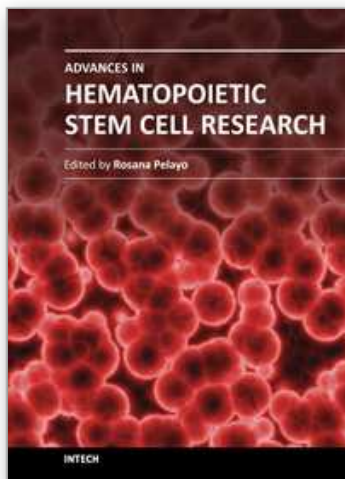
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This book provides a comprehensive overview in our understanding of the biology and therapeutic potential of hematopoietic stem cells, and is aimed at those engaged in stem cell research: undergraduate and postgraduate science students, investigators and clinicians. Starting from fundamental principles in hematopoiesis, Advances in Hematopoietic Stem Cell Research assemble a wealth of information relevant to central mechanisms that may regulate differentiation, and expansion of hematopoietic stem cells in normal conditions and during disease.

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