Chapter 6
Indications for Hematopoietic Stem Cell Transplantation in Children

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Introduction

The past few years have seen dramatic changes in the field of pediatric hemato-oncology, due to both significant advances in transplantation techniques and the introduction of new targeted therapies, thus modifying the position of hematopoietic stem cell transplantation (HSCT) in the therapeutic armamentarium for childhood hematologic malignancies.

Guidelines on the indications for allogeneic (allo-HSCT) and autologous HSCT (auto-HSCT) have been released by the American Society for Blood and Marrow Transplantation (ASBMT) [1] and the European Society for Blood and Marrow Transplantation (EBMT) [2] (Table 6.1).

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É. Gluckman et al. (eds.), *Establishing a Hematopoietic Stem Cell Transplantation Unit*, https://doi.org/10.1007/978-3-319-59358-6_6

Table 6.1 Indications for allogeneic and autologous HSCT (adapted from [1, 2])

Disease	Disease status	Allogeneic HSCT		Autologous HSCT	
Hematological malignancies		EBMT	ASBMT	EBMT	ASBMT
Acute lymphoblastic leukemia	CR1 (HR)	S	S	N	N
	CR2	S	S	N	N
	Subsequent CR	S	S	N	N
	No remission	–	S	–	N
Acute myeloid leukemia	CR1 (HR)	S	S	C	N
	CR2	S	S	C	N
	Subsequent CR	S	S	N	N
	No remission	S	S	–	N
	APL, relapse	–	R	–	R
Chronic myeloid leukemia	First chronic phase failing TKI	C	S	N	N
	Accelerated phase	C	S	N	N
	Blast phase	–	S	–	N
Myelodysplastic syndromes	Low risk	S	S	N	N
	High risk	S	S	N	N
	JMML	S	S	N	N
	Therapy related	S	S	N	N
Hodgkin lymphoma	Primary refractory	–	S	–	[a]
	First relapse	C	S	S	[a]
	Second or greater relapse	C	S	S	[a]
Non-Hodgkin lymphoma (NHL)					
T-cell NHL	CR1 (high risk)	C	S	C	N
	CR2	S	S	C	N
	Subsequent CR	–	S	–	N
	No remission	–	S	–	N
Lymphoblastic B-cell NHL	CR1 (high risk)	C	S	C	N
	CR2	S	S	C	N
	Subsequent CR	–	S	–	N
	No remission	–	S	–	N
Burkitt's lymphoma	First or greater relapse	S	S	C	[a]
Anaplastic large cell lymphoma	Primary refractory	–	S	–	[a]
	First relapse	S	S	C	[a]
	Second or greater relapse	S	S	C	[a]
Non-malignant disorders		*EBMT*	*ASBMT*	*EBMT*	*ASBMT*
Severe combined immunodeficiency		S	R	N	N
Wiskott-Aldrich syndrome		S	R	N	N
Chronic granulomatous disease		S	R	N	N

Table 6.1 (continued)

Disease	Disease status	Allogeneic HSCT		Autologous HSCT	
Hematological malignancies		EBMT	ASBMT	EBMT	ASBMT
Severe congenital neutropenia		S	R	N	N
Hemophagocytic disorders		S	R	N	N
Other phagocytic cell disorders		S	R	N	N
Thalassemia		S	S	N	N
Sickle cell disease		S	S	N	N
Severe aplastic anemia	Newly diagnosed	S	S	N	N
	Relapsed/ refractory	S	S	N	N
Fanconi anemia		S	R	N	N
Dyskeratosis congenita		–	R	–	N
Blackfan-Diamond anemia		–	R	–	N
Congenital amegakaryocytic thrombocytopenia		–	R	–	N
MPS-1H Hurler syndrome		S	R	N	N
MPS-1H Hurler Scheie syndrome (severe)		–	–	–	N
MPS-VI Maroteaux- Lamy syndrome		C	R	N	N
Osteopetrosis		S	R	N	N
Globoid cell leukodystrophy (Krabbe)		–	R	–	N
Metachromatic leukodystrophy		–	R	–	N
Cerebral X-linked adrenoleukodystrophy		–	R	–	N
Solid tumors		C	D	S/C	S

[a]Depending on disease chemosensitivity

N not generally recommended, *S* standard of care, *C* clinical option, *D* developmental, *R* rare indication. *HSCT* hematopoietic stem cell transplantation, *CR* complete remission, *HR* high-risk, *APL* acute promyelocytic leukemia, *TKI* tyrosine kinase inhibitor, *JMML* juvenile myelomonocytic leukemia, *NHL* non-Hodgkin lymphoma, *EBMT* European Society for Blood and Marrow Transplantation, *ASBMT* American Society for Blood and Marrow Transplantation, *MPS* Mucopolysaccharidoses

Hematological Malignancies

Acute Lymphoblastic Leukemia (ALL)

Current frontline chemotherapy protocols for children with newly diagnosed acute lymphoblastic leukemia (ALL) can now cure more than 80% of patients [3]. Nonetheless, for subsets of children with high-risk (HR) features, identified by poor early response to therapy and/or genetic characteristics of leukemia cells, as well as for patients who experience disease relapse, outcomes are significantly worse.

The therapeutic advantage of allo-HSCT as a post-remission/consolidation strategy for these patients lies not only in the possibility to administer a more intensive treatment during the conditioning regimen, but also in the antileukemia alloreactions mediated by the graft.

Indications for HSCT in First Complete Remission (CR1)

The role of HSCT as a consolidation strategy in the frontline treatment of pediatric ALL must be considered in the context of a risk-stratified approach, based upon prognostic factors that can drive treatment intensity, with the aim of optimizing outcomes, while reducing unnecessary toxicities. The definition of these prognostic factors (namely, cytogenetic/molecular abnormalities at diagnosis and the response to induction treatment) is the result of the remarkable knowledge gathered from a series of large-scale analyses conducted by international cooperative groups.

HSCT in children with ALL in CR1 is currently reserved for subsets of patients with HR features.

In 2005, the International Berlin-Frankfurt-Münster (BFM) Study Group and the Pediatric Working Party of the EBMT Group reported the results of a cooperative prospective study comparing chemotherapy versus allo-HSCT from a human leucocyte antigen HLA–matched family donor (MFD) for very-HR childhood ALL in CR1, defined by the presence of at least one of the following criteria: (1) failure to achieve post-induction CR; (2) t(9;22) or t(4;11) clonal abnormality; (3) poor response to a 7-day prednisone prephase, associated with T-immunophenotype, white blood cell count (WBC) of 100×10^9/L or greater, or both. Five-year disease-free survival (DFS) was 40.6% in children allocated to chemotherapy and 56.7% in those given HSCT ($p = 0.02$). The 5-year overall survival (OS) estimate in children assigned to chemotherapy or HSCT was 50.1% and 56.4%, respectively ($p = 0.12$) [4].

A large prospective clinical trial has demonstrated that standardized quantitative assessment of minimal residual disease (MRD), using quantitative polymerase chain reaction (PCR) analysis of immunoglobulin gene rearrangements, measured at two time points (TPs) during induction treatment (TP1: day 33; TP2: day 78), can provide risk stratification of children with B-cell precursor (BCP) ALL and affect the choice of post-induction treatment [5]. Patients were considered MRD standard-risk (SR) if negative for MRD at both time points; MRD intermediate-risk (IR) if positive either at day 33 or day 78 and $<10^{-3}$ leukemic cells at day 78; and MRD HR if positive $\geq 10^{-3}$ leukemic cells at day 78. In the multivariate analysis, PCR-MRD was observed to be the most relevant factor for discriminating prognosis. The 5-year event-free survival (EFS) estimates for MRD-SR, MRD-IR, and MRD-HR patients were 92.3%, 77.6%, and 50.1%, respectively, with 5-year OS probabilities of 97.8%, 93.4%, and 60.8%, respectively. High levels of MRD at TP2 were predictive of poor outcome (5-year EFS < 50%). Fast clearance of MRD was associated with a favorable prognosis independently of non-MRD-related risk features, suggesting that, in patients undergoing relatively intensive treatment, if the MRD response is favorable, HSCT may not be indicated, even in the presence of any other combination of risk factors. On the other hand, for patients with a poor MRD response (i.e., MRD $\geq 10^{-3}$ leukemic cells after 2 months of therapy) despite favorable non-MRD risk criteria,

treatment intensification with HSCT may be indicated to compensate for the MRD-derived high risk of relapse.

The outcome of the cohort of HR patients enrolled in the Associazione Italiana Ematologia e Oncologia Pediatrica (AIEOP)-BFM ALL2000 study has been recently reported [6]. The statistical comparison of HSCT versus chemotherapy, accounting for waiting time to transplantation, did not show a significant advantage for HSCT over chemotherapy in terms of DFS. Nonetheless, in the larger subgroup of patients (subgroup 2), characterized by MRD-HR $\geq 5 \times 10^{-4}$ and $< 5 \times 10^{-3}$ leukemic cells at TP2 or by the presence of t(4;11) and prednisone good response, the initial advantage of chemotherapy changed to a disadvantage in favor of HSCT as time increased, due to late relapses after chemotherapy. Patients with T-cell lineage ALL belonging to subgroups 2 and 3 (MRD-HR $\geq 5 \times 10^{-3}$ leukemic cells at TP2 or no remission at day +33 or the presence of t(4;11) and poor prednisone response) seemed to benefit from HSCT in terms of both DFS and OS.

The current approach of the AIEOP-BFM treatment scheme is to emphasize the role of MRD kinetics in the choice of the HSCT strategy in CR1 (see also Table 6.2).

Distinct mention needs to be made of two particular conditions:

- BCR/ABL-positive ALL with poor early response.
- ALL diagnosed within the first 12 months of life ("infant ALL") harboring rearrangements of the mixed-lineage-leukemia (MLL) gene.

In the pre-tyrosine kinase inhibitor (TKI) era, the prognosis of BCR/ABL-positive ALL was dismal, with low survival rates even with the combination of chemotherapy and HSCT. The introduction of TKIs into HR ALL chemotherapy backbones deeply modified the history of BCR/ABL-positive ALL.

Table 6.2 Indications for allogeneic HSCT according to the current BFM-AIEOP ALL 2009 study protocol

	PCR-MRD results				
			MRD-HR		
Risk factor	MRD-SR	MRD-MR[a]	MRD TP2 $\geq 10^{-3}$ to $<10^{-2}$ leukemic cells	MRD TP2 $\geq 10^{-2}$ leukemic cells	No MRD results
No CR day 33	No	MMD	MMD	MMD	MMD
t(4;11)	No	MD	MD	MMD	MD
Hypodiploid karyotype <44 chromosomes	No	MD	MD	MMD	MD
Poor prednisone response T-ALL	No	No	MD	MMD	MD
None of the above-mentioned features	No	No	MD	MMD	No

[a]Including MRD-MR patients who are slow early responders (MRD TP1 $\geq 10^{-3}$ leukemic cells and TP2 $10^{-4/-5}$ leukemic cells)

ALL acute lymphoblastic leukemia, *BFM-AIEOP* Berlin-Frankfurt-Münster-Associazione Italiana Ematologia e Oncologia Pediatrica International, *PCR-MRD* polymerase chain reaction-based minimal residual disease, *TP1* timepoint 1 (day 33), *SR* standard risk, *MR* medium risk, *HR* high risk, *CR* complete remission, *no* no indication for HSCT, *MD* HLA-matched donor, *MMD* HLA-mismatched donor

In 2009, the Children's Oncology Group (COG) reported data on the use of imatinib, progressively increased in five patient cohorts from 42 (cohort 1) to 280 continuous days (cohort 5), combined with an intensive chemotherapy regimen, in 92 BCR/ABL-positive ALL patients aged 1–21 years. The addition of imatinib improved the outcome in cohort 5 patients, who achieved a 3-year EFS of 80%, higher than that of historical controls (35%; $p < 0.0001$) and comparable to that of MFD or HLA-matched unrelated donor (MUD)-HSCT recipients [7].

In 2012, the results of a large collaborative European trial (EsPhALL) were reported [8]. Patients were classified as good risk or poor risk according to early response to induction treatment. Allo-HSCT was recommended for all poor-risk patients, from any type of donor, and for good-risk patients with any genotype-matched donor, and was performed in CR1 in 137 out of 178 (77%) patients. In both the good- and poor-risk groups, the outcomes of patients given imatinib without transplantation appeared to be poorer than those of HSCT recipients.

The current approach in the treatment of Philadelphia chromosome (Ph)-positive ALL emphasizes MRD monitoring in the therapeutic decision-making process. An ongoing combined follow-up study (ClinicalTrials.gov Identifier: NCT01460160), assessing the effect of earlier, continuous exposure to dasatinib, is pursuing the transplant approach in CR1 only in patients who fail to meet predefined MRD criteria and who have an HLA-matched donor.

The prognosis of infant ALL is still relatively poor if compared with that of older children with ALL, achieving EFS probabilities of about 40–50% with current therapies [9]. Treatment protocols developed in the past 10–15 years have been investigating strategies to improve outcomes, such as treatment intensification with hybrid protocols including both lymphoblastic- and myeloid-oriented regimens, or the use of HSCT in CR1 [9, 10]. The potential benefits of HSCT for treating patients in this extremely vulnerable age group must be carefully weighed against the risk of long-term effects of the conditioning regimen on growth and development, requiring us to limit the transplant indication to infants with a poor probability of maintaining remission with chemotherapy alone.

In infants with MLL-positive ALL, a significant difference in DFS between patients receiving HSCT and those given chemotherapy alone was reported by the Interfant-99 Study Group. Furthermore, in the subgroup of infants younger than 6 months and with either prednisone-poor response or leukocytes $\geq 300 \times 10^9$ cells/L, HSCT was associated with a 64% reduction in the risk of failure resulting from relapse or death in CR, while in the remaining patients, no advantage for HSCT over chemotherapy alone was observed [11].

The current International Collaborative Treatment Protocol for Infants (Interfant06; ClinicalTrials.gov Identifier: NCT00550992) identifies three risk groups, based upon MLL status, age, and WBC at diagnosis/prednisone response. All HR patients (infants with MLL rearrangement, age < 6 months, and either WBC $> 300 \times 10^9$/L or prednisone-poor response) are considered eligible for HSCT, whereas in the MR group (remaining MLL-rearranged patients) HSCT is indicated only in those with MRD level $> 10^{-4}$ leukemic cells at the end of consolidation.

Indications for HSCT in Second (CR2) or Subsequent Complete Remission

While the prognosis of newly diagnosed childhood ALL has dramatically improved, the outcome of children with relapsed ALL remains unsatisfactory. At relapse, about 30–50% of the children can be rescued with high-dose chemotherapy regimens, in most cases followed by allo-HSCT.

Factors identified to be predictors of outcome in relapsed ALL, and thus critical in the identification of patients who can be rescued with chemotherapy alone and those in need of allo-HSCT, are the time to relapse (very early, early, or late), the site of relapse (isolated bone marrow [BM], combined, or isolated extramedullary relapse), and the immunological lineage of the disease (BCP vs. T-lineage ALL) [12]. Combining these risk factors, a classification into four different risk groups has been proposed to stratify patients with relapsed ALL in order to deliver risk-adapted treatments. Details of this classification, together with its prognostic impact, are reported in Table 6.3.

Allo-HSCT from an MFD is able to guarantee a higher EFS probability in comparison to that achieved with second-line chemotherapy [13]. Some studies suggested that the advantage of HSCT over chemotherapy alone could be limited to specific subgroups, e.g., patients with HR relapse (S3/4 group) or IR relapse [14], or patients experiencing disease recurrence within 36 months from diagnosis and receiving a total body irradiation-based conditioning regimen [15].

In patients with a standard risk profile (SR or S1/2), HSCT should be offered to those with BM involvement and MRD poor response after salvage induction therapy.

Thanks to the dramatic advances achieved in the field of allo-HSCT, outcomes after MUD-HSCT now approach those obtained in the MFD setting [16]. A matched-pair analysis from the BFM group, comparing MUD-HSCT with chemotherapy for children with ALL in CR2, documented a significantly higher EFS probability for the HR subgroup (44% vs. 0%), but not for IR patients (39% vs. 49%) given HSCT [17].

Table 6.3 BFM classification of relapsed childhood ALL (modified from [12])

S1–S4 group	Patients (%)	Definition of relapse	5-Year OS with chemotherapy (%)	5-Year OS with HSCT (%)
S1	5	1. Late extramedullary relapses	60–70	Not employed
S2	55	1. Early extramedullary relapses	40	60
		2. Very early extramedullary relapses		
		3. Non-T late BM relapses		
		4. Non-T combined early/late relapses		
S3	15	1. Non-T early BM relapses	<5	30
S4	25	1. Very early BM relapses	<5	25
		2. Very early combined relapses		
		3. T-phenotype BM relapses		

BM *bone marrow*, *OS* overall survival, *very early relapse*, <18 months from diagnosis*; early relapse*, >18 months from diagnosis, but <6 months from treatment discontinuation; *late relapse*, >6 months from treatment discontinuation; *S1-S4:* stratification groups (*S1,* standard risk*; S2,* intermediate risk*; S3, S4,* higher risk)

Current outcomes after umbilical cord blood transplantation (UCBT) have been observed to be similar to those obtained with unrelated BM grafts [18]. A retrospective analysis of children with ALL given unrelated UCBT reported to the Eurocord Registry documented a 4-year EFS of 44%, with high levels of pre-HSCT MRD predicting an increased risk of relapse [19].

The significant advances also achieved in the haploidentical setting have significantly broadened the applicability of HSCT, with outcomes currently approaching those obtained in the matched-donor setting.

In patients with ALL in CR3, the use of sole chemotherapy is associated with a very high risk of subsequent relapse; however, it has to be mentioned that allo-HSCT can also result in a considerable risk of transplant-related mortality (TRM), due to the pre-existing cumulative treatment toxicity.

Acute Myeloid Leukemia (AML)

The past two decades have seen a significant improvement in the outcomes of children with newly diagnosed acute myeloid leukemia (AML) [20], as a result of multiple factors, including advances in supportive care, progressive acquisitions of cytogenetic/molecular markers that have refined patient risk stratification, and the broad use of HSCT as consolidation strategy [21].

As in ALL, the therapeutic potential of HSCT results from both the possibility of delivering an intensive treatment before the allograft and the immunologic effect of the graft towards residual AML.

Indications for HSCT in First Complete Remission (CR1)

Allo-HSCT has been shown to be the most effective post-remission therapy for children with AML in CR1 when an MFD is available, in particular in patients with HR features [21], in whom transplantation is able to lower the relapse incidence to an extent comparable to that in SR children [22]. Thanks to the introduction of high-resolution HLA-typing, allowing a dramatic improvement in outcomes after transplantation from unrelated volunteers, indications for MUD-HSCT now partially coincide with those for MFD-HSCT.

In protocols in which the sole indication for HSCT was the availability of an MFD, a higher DFS was documented in patients transplanted in CR1, in comparison with patients receiving sole chemotherapy, without any difference in OS [23, 24].

More recently, a risk-stratified approach is being used, and candidates for HSCT in most current cooperative protocols are identified by the presence of HR features (i.e., unfavorable cytogenetic/molecular characteristics of leukemia cells and/or poor MRD clearance during induction therapy) [20].

Indications for HSCT in pediatric AML in CR1 are summarized in Table 6.4.

Genetic characterization of AML blast cells represents a major criterion for risk assessment at diagnosis, as first documented by the Medical Research Council (MRC) AML 10 trial [34].

Table 6.4 Indications for HSCT and proportion of patients given allo-HSCT in CR1 in recently reported pediatric AML trials (modified from [25])

Protocol	HSCT indications	Donor	Allo-HSCT (%)	Reference number
AIEOP AML 2002/01	HR patients (all patients except those with t(8;21) and inv.(16) and those in morphologic CR after the first of two induction courses)	MFD	29	[22]
		Auto-HSCT if MFD not available		
BFM 2004	HR patients (all patients except those with FAB M1/M2 with Auer rods, FAB M4eo or favorable cytogenetics [t(8;21) or inv.(16)] and blasts in BM on day 15 < 5%, FAB M3). From 2006 only no CR after 2nd induction	MFD	18	[26, 27]
COG CCG-2891	All patients with an available MFD	MFD	15	[28]
JPLSG AML99	IR and HR patients (all patients except for those with t(8;21) and WBC < 50,000/μL, inv.(16), or age < 2 years without HR factors)	MFD for IR patients MFD or MUD for HR patients	15	[29]
LAME 89/91	All patients with an available MFD	MFD	23	[30]
MRC AML 12	All patients except for those with t(8;21), inv.(16), t(15;17), or FAB M3, irrespective of BM status after course 1	MFD	11	[31]
NOPHO 2004	Poor response to induction (>15% blasts at day 15 after 1st induction or no CR after 2nd induction) or *MLL* rearrangements other than t(9;11)(p21;q23)	MFD or MUD	13	[32]
	From 2009: poor response to induction, only			
St Jude AML 02	SR patients with an available MFD	MFD for SR patients	25	[33]
	HR patients (monosomy 7, *FLT3*-ITD, t(6;9), FAB M7, treatment-related AML, AML secondary to MDS or >25% blasts after induction I or persistent MRD after three courses of therapy)	MFD or MUD for HR patients		

AML acute myeloid leukemia, *AIEOP* Associazione Italiana di Ematologia e Oncologia Pediatrica, *BFM* Berlin-Frankfurt-Münster, *CCG* Children's Cancer Study Group, *COG* Children's Oncology Group, *JPLSG* Japanese Paediatric Leukaemia/Lymphoma Study Group, *LAME* Leucemie Aique Myeloide Enfant, *MRC* Medical Research Council, *MDS* myelodysplastic syndromes, *MFD* HLA-matched family donor, *MLL* mixed-lineage-leukemia, *NOPHO* Nordic Society for Pediatric Haematology and Oncology

Core-binding factor abnormalities, such as t(8;21) or inv.(16), identified a group of patients with a relatively favorable prognosis, while in patients lacking these favorable changes, the presence of a complex karyotype, monosomy 5, del(5q), monosomy 7, or abnormalities of 3q was found to predict a poor outcome.

More recently, other cytogenetic/molecular prognostic markers were identified [25]. In the favorable group, t(1;11)(q21;q23), normal karyotype with *NPM1* mutation, and double mutant *CEBPA* were reported. Among adverse cytogenetic features, the following abnormalities have been associated with poor prognosis: del(7q); KMT2A (MLL) aberrations, excluding t(9;11)(p21;q23) and t(11;19)(q23;p13), t(9;22)(q34;q11), −17; and abnormalities of 12p, t(6;9), t(7;12), del(12p). A very poor outcome has been reported in the presence of the NUP98/NSD1 fusion gene, often associated with Fms-like tyrosine kinase 3 (FLT3)-internal tandem duplication (ITD) [35].

Considering that morphological CR is achieved in more 90% of children after induction therapy, but that relapse occurs in 30–40% of patients, the monitoring of MRD during treatment may allow the identification of patients at higher risk of relapse. A benefit of HSCT compared with chemotherapy alone has been reported in patients with poor MRD clearance, in particular when MRD levels remain above 1% after the first induction course [33]. For this reason, MRD monitoring has been included in many current protocols for the treatment of newly diagnosed pediatric AML, in order to refine patient stratification to receive HSCT in CR1.

The outcomes of children with HR-AML in CR1 given either auto- or allo-HSCT (based on the availability of an MFD) in the AIEOP AML 2002/01 Study Protocol were recently reported. Patients with M7 FAB subtype, complex karyotype or FLT3-ITD, were eligible for HSCT from alternative donors. The 8-year probability of DFS was 73.8% for recipients of MFD allografts, while for patients given MUD-HSCT, DFS was 75.5% in BM recipients, 53% in peripheral blood stem cell (PBSC) recipients, and 92.3% when UCB cells were employed (overall $p = 0.0035$) [36].

Indications for HSCT in Second (CR2) or Subsequent Complete Remission

Allo-HSCT represents the best chance of cure in children with AML in CR2. Patients with favorable cytogenetic/molecular characteristics, long duration of CR1, not receiving HSCT in CR1, and with good response to reinduction therapy have a higher probability of being rescued by transplantation in CR2 [37].

Patients not given HSCT in CR1 and who receive HSCT in CR2 have a 5-year OS approaching 60%, whereas in those relapsing after HSCT performed in CR1, poor outcomes have been reported [38].

Acute Promyelocytic Leukemia (APL)

Given the excellent results obtained since the introduction of all-*trans*retinoic acid (ATRA) in the treatment of APL, HSCT is currently not indicated in CR1. In patients with relapsed/refractory APL, the current role of HSCT as post-remission/consolidation strategy is controversial, as most reports of HSCT for APL in CR2 were published before the introduction of arsenic trioxide (ATO). Furthermore, as relapse incidence is very low in the ATRA and ATO era, randomized trials to compare different consolidation approaches in CR2 appear hardly feasible.

Experience with HSCT in treating pediatric relapsed APL is limited, the majority of data having been obtained from small retrospective studies. Data from the largest published series documented a 5-year EFS in the order of 70% for both auto- and allo-HSCT, with an incidence of TRM after auto- and allo-HSCT of 0% and 19%, respectively, all treatment-related deaths occurring in the early study period, before 1996. Relapse occurred in 27% of autografted patients and 10% of allo-HSCT recipients [39]. Even though the success of allo-HSCT is hampered by a higher risk of TRM, if compared with auto-HSCT, its use can provide a lower relapse incidence, probably due to the Graft versus Leukemia (GvL) potential of the donor graft against residual APL.

An expert panel of members from the COG and the International BFM Study Group recently published recommendations for the management of relapsed and refractory childhood APL. The authors suggest considering allo-HSCT in patients with prior ATO exposure, in patients with short duration of CR1, in patients with primary refractory disease, in those in second or further relapse, or those not achieving molecular CR after four salvage cycles. Auto-HSCT appears to be a reasonable option for treatment consolidation for ATO-naïve patients who achieve a second molecular CR after four salvage cycles [40].

Chronic Myeloid Leukaemia (CML)

In the pre-TKI era, allogeneic HSCT was the standard of care for children with Ph+ chronic myeloid leukemia (CML). The introduction of TKIs into the treatment of Ph + CML deeply modified the history of the disease, leading to a significant decrease in the use of HSCT. Nonetheless, based on currently available data, no certain evidence of the complete eradication of the Ph + clone by prolonged treatment with TKIs exists. Furthermore, the long-life expectancy of pediatric patients, entailing the need for potentially life-long treatment, renders the alternative choice between TKIs and transplantation controversial.

Current algorithms for the management of children with newly diagnosed CML in chronic phase (CP) include frontline treatment with hydroxyurea and a first-generation TKI, with a switch to a second-generation TKI in cases of failure to obtain an acceptable response. Allo-HSCT is reserved for patients who experience progression or relapse or persistently high levels of the BCR/ABL fusion transcript on second-generation TKI treatment. For children presenting with CML in accelerated phase or blast crisis, initiation of TKI therapy is recommended, followed by allo-HSCT once a reversion to chronic phase has been obtained [41].

Myelodysplastic Syndromes and Myeloproliferative Neoplasms

Myelodysplastic syndromes (MDSs) encompass a group of clonal disorders of HSCs and their precursors, characterized by peripheral cytopenia, dysplasia in one of the myeloid lineages with ineffective hematopoiesis, and a variable propensity to

evolve towards acute leukemia. The classification of pediatric MDSs includes low-grade forms (refractory cytopenia of childhood; RCC) and advanced MDSs; namely, refractory anemia with excess blasts (RAEB) and RAEB in transformation (RAEB-t). MDSs are rare in children, accounting for about 5% of hematologic malignancies, and they can be part of the natural evolution of inherited BM failure syndromes.

As childhood MDSs show relatively poor responses to conventional chemotherapy [42] and pre-transplant chemotherapy is not associated with improved outcomes [43], HSCT should be considered early in the course of the disease. Commonly accepted indications include advanced MDSs (i.e., RAEB and RAEB-t), MDS secondary to chemo-radiotherapy, and RCC associated with either cytogenetic anomalies (e.g., monosomy 7, complex karyotype) or severe neutropenia or transfusion dependence [43].

The results of the European Working Group on Childhood MDS (MDS) 98 study, which enrolled 97 patients with RAEB, RAEB-t, and myelodysplasia-related AML given HSCT from an MFD ($N = 39$), MUD ($N = 57$), or alternative family donor ($N = 1$), were recently reported. The 5-year probability of OS was 63%, with a 21% cumulative incidence of TRM and relapse. Factors associated with increased TRM were age at HSCT >12 years, time from diagnosis to HSCT longer than 4 months, and occurrence of acute or extensive chronic graft-versus-host disease (GVH-D) [43].

Monosomy of chromosome 7 or partial deletion involving its long arm [del(7q)] are recurrent chromosomal aberrations in RCC and have been reported to be associated with a significantly higher probability of progression to advanced MDS [44]. Moreover, a significantly better probability of survival has been shown in patients transplanted before evolution to advanced MDS in comparison to patients experiencing disease progression (76% vs. 36%, respectively, $p = 0.03$) [44].

For this reason, children with RCC and monosomy 7, del(7q), or a complex karyotype should be offered transplantation from either an MFD or a MUD early in the course of the disease. Conversely, children with RCC and normal karyotype or chromosomal abnormalities other than monosomy 7, del(7q) or a complex karyotype may experience a long, stable disease course, allowing a “watch and wait” approach. By virtue of the low TRM rates of MFD-HSCT, transplantation may be recommended for children with an available HLA-identical sibling. For patients lacking such a donor but experiencing transfusion dependence, severe neutropenia, or infections, transplantation from a MUD should be offered. A valid alternative is represented by immunosuppressive therapy (IST), with cyclosporine, antithymocyte globulin (ATG), and steroids.

Juvenile myelomonocytic leukemia (JMML) is an aggressive clonal hematopoietic disorder of infancy and early childhood, with features straddling myeloproliferative neoplasms and MDS. Approximately 90% of children with JMML carry either somatic or germline mutations in genes involved in the RAS/mitogen-activated protein kinase (MAPK) pathway, such as PTPN11, NRAS, KRAS, CBL, or NF1. Although spontaneous resolution has been rarely described, allogeneic

Table 6.5 Indications for HSCT in genetic subgroups of JMML (modified from [45])

	PTPN11	K-RAS	N-RAS	NF1	CBL
Germline mutations	"Watch and wait" (Noonan syndrome)	"Watch and wait" (Noonan syndrome)	"Watch and wait" (Noonan syndrome)	HSCT (neurofibromatosis type 1)	"Watch and wait" HSCT only if disease progression occurs (CBL syndrome)
Somatic mutations	HSCT from either an MFD or a MUD	HSCT from either an MFD or a MUD	HSCT from either an MFD or a MUD for most patients		

HSCT remains the treatment of choice for most JMML patients, being able to cure more than 50% of such patients. Prompt HSCT is recommended for all children with JMML and NF-1, somatic PTPN-11 mutations, and K-RAS mutations, and for the majority of children with somatic N-RAS mutations (Table 6.5). Conversely, because spontaneous regression of myeloproliferation has been observed in children with germline CBL mutations, as well as in Noonan syndrome patients, a "watch and wait" strategy is appropriate in these cases [45].

Disease recurrence is the main cause of treatment failure in patients given allogeneic HSCT for JMML. Thus, strategies aimed at optimizing the GvL effect, such as, whenever possible, a rapid tapering and discontinuation of GVH-D prophylaxis after transplantation, are recommended in children with JMML.

Pediatric Lymphomas

Given the excellent outcomes achieved with current risk-adapted first-line therapy for both pediatric Hodgkin lymphoma (HL) and non-Hodgkin lymphomas (NHLs), there is no indication for HSCT during frontline treatment for either of these entities [46]. However, primary refractory disease or relapse can occur in up to 10–15% of children, for whom a dismal prognosis has been reported [47]. For those patients, both autologous and allogeneic HSCT have become part of salvage therapy strategies.

Data on children with lymphoma treated with high-dose chemotherapy followed by autologous stem cell rescue, as well as data on allo-HSCT, are limited to small case series, with heterogeneous pre-transplant chemotherapy and conditioning regimens. Historically, auto-HSCT has been preferred to allo-HSCT because of easier stem cell availability and a lower rate of TRM [46]. In a large EBMT registry-based analysis, including both pediatric and adult patients, and comparing allo-HSCT with auto-HSCT, the advantage of allo-HSCT, in terms of disease recurrence, was counterbalanced by a high incidence of treatment-associated complications,

resulting in a higher OS after auto-HSCT [48]. Nonetheless, with recent advances in allo-HSCT techniques (including high-resolution HLA-typing, improvements in supportive care, and the implementation of less toxic conditioning regimens), this approach is being increasingly used in children with lymphomas.

Hodgkin Lymphoma

In adult patients, high-dose chemotherapy followed by the infusion of autologous HSCs has been shown to be superior to chemotherapy alone in randomized controlled trials including relapsed and primary refractory HL [49]. The improvement in progression-free survival (PFS) was particularly evident in patients with disease recurrence within 1 year after the end of treatment (41% for auto-HSCT vs. 12% for chemotherapy alone, $p = 0.008$), but was still significant for patients with later relapse (75% vs. 44%, $p = 0.025$). Based on these results, auto-HSCT has also been increasingly used as salvage therapy in children with poor-risk features. Indeed, even among patients with HR HL with a first relapse, salvage therapies including auto-HSCT can result in long-term cure in approximately 50% of cases [50].

In a recent retrospective analysis from the Center for International Blood and Marrow Transplant Research (CIMBTR) on 606 Childhood, Adolescent and Young Adult (CAYA) patients, performance status at the time of HSCT, no extranodal involvement, and chemosensitivity were associated with a significantly improved PFS, while patients with time from diagnosis to first relapse shorter than 1 year had a significantly inferior PFS [51].

Due to a reported higher rate of TRM in allo-HSCT than in auto-HSCT [48], the role of allo-HSCT in HL is still controversial, both in adults and the CAYA population. However, a meta-analysis showed a reduced (up to 5–10% lower) non-relapse mortality (NRM) with increased PFS and OS (up to 15–20% higher) in recent studies (i.e., those starting accrual in 2000 or later) [52]. The largest study reporting data for children and adolescents given allo-HSCT showed an NRM of 21%, with comparable results after reduced-intensity conditioning (RIC) or a myeloablative conditioning (MAC) regimen [53]. Relapse incidence was increased after RIC compared with MAC, thus resulting in a better PFS for patients given MAC (40 vs. 30%, $p = 0.02$). Of note, while no difference in outcome was observed between MFD and MUD-HSCT, the use of mismatched donors significantly reduced PFS after HSCT. Unmanipulated haploidentical BM transplantation with post-transplantation cyclophosphamide showed good results in patients with advanced HL [54].

Non-Hodgkin Lymphoma (NHL)

In children and adolescents the four most frequent subtypes of NHL are Burkitt (BL), lymphoblastic (LBL), diffuse large B cell (DLBCL), and anaplastic large cell lymphoma (ALCL). Despite very good results obtained with first-line therapies, with long-term EFS up to 90%, depending on histological subtype [55], the

prognosis of relapsed or refractory NHL is dismal, with the only exception being ALCL [56]. In adults, auto-HSCT has been proven to be superior to chemotherapy alone for the treatment of relapsed NHL [57], but no clear indications exist for selecting autologous or allogeneic HSCT.

The role of auto- and allo-HSCT is also still unclear in children with NHL. A recent registry-based study examined the role of HSCT in 182 patients affected by BL, LBL, DLBCL, and ALCL, given autologous (N = 90) or allogeneic HSCT (N = 92) from an MFD (N = 43) or a MUD (N = 49) [58]. After adjusting for disease status, no difference in 5-year EFS was observed between allo- and auto-HSCT for BL, DLBCL, or ALCL, while the outcome of relapsed/refractory LBL was superior after allo-HSCT [58].

A promising approach is the combination of MAC auto-HSCT, followed by a RIC allo-HSCT, which has been reported to allow a 10-year EFS of 70% [59].

Some children with NHL have a pre-existing condition predisposing to lymphoma (e.g., cancer predisposition syndromes or primary immune deficiencies). Because these patients suffer from increased treatment-related toxicities (leading to an inferior survival rate), special vigilance should be exerted when they are receiving chemotherapy or undergoing auto- or allo-HSCT [60].

Non-malignant Disorders

Primary Immune Deficiencies

Since the first successful attempt was made to cure primary immune deficiencies (PIDs) with HSCT, many significant changes have been made in transplant indications and techniques for these disorders. While the management of some PIDs is still based on conservative approaches, for other disorders HSCT is now becoming a widely accepted treatment strategy.

Taking into consideration the wide clinical heterogeneity of patients, the consensus of the EBMT and the European Society for Immunodeficiencies (ESID) is that each case should be carefully evaluated for indications and transplant strategy, in a center with significant experience [61].

Apart from severe combined immune deficiencies (SCIDs), for which there is a clear recommendation for HSCT [62], transplantat indications for non-SCID PIDs are being debated. Among the non-SCID PIDs, successful HSCTs have been performed in Wiskott-Aldrich syndrome (WAS), chronic granulomatous disease (CGD), hemophagocytic syndromes (such as hemophagocytic lymphohistiocytosis [HLH] and X-linked lymphoproliferative syndromes [XLP1 and XLP2], CD40-ligand deficiency, DNA repair disorders (such as ligase 4 deficiency, Cernunnos syndrome, and Nijmegen breakage syndrome), DOCK8 deficiency, and immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome [63].

Until recent years, the availability of an HLA-identical related donor was one of the main factors influencing the choice of transplantation in PIDs. However, the introduction of high-resolution molecular HLA-typing [64], together with

the optimization of graft manipulation techniques, has broadened transplant access for these disorders [65]. Prognosis after HSCT for PIDs (influencing the decision to offer a transplantation) is dependent on the molecular defect at the basis of the disorder, disease status, donor type, HSC source, and the conditioning regimen [66].

Further, the increasing interest in gene therapy for the cure of PIDs is likely to render the therapeutic decision-making process and the definition of clear indications for HSCT more complex in coming years.

Hemoglobinopathies Disorders

The past 30 years have witnessed significant advances in supportive care and interventional therapies for thalassemia major (TM) and sickle cell disease (SCD). This has led to improved quality of life and survival rates for TM and SCD patients in many high-income countries, but has simultaneously brought about new medical needs associated with the progressive development of chronic disease and/or treatment-related complications. Conversely, in developing countries these disorders still represent a relevant cause of childhood mortality.

While the recent advances in gene-therapy approaches are likely to allow the forthcoming translation of promising preclinical and clinical evidence into a viable reality, at present allogeneic HSCT is the only consolidated possibility of definitive cure for hemoglobinopathies.

The widest experience of HSCT in these diseases has been obtained using BM cells harvested from an HLA-identical sibling donor. In this setting, major recently published studies report OS and DFS probabilities of over 90% and 85%, respectively, for TM, and more than 90% and 80%, respectively, for SCD [67, 68].

In 2014, a consensus document with recommendations on current HSCT strategies for TM and SCD was published by an expert panel selected by the EBMT Paediatric Diseases Working Party and Inborn Error Working Party [69].

Thalassemia Major

As indicated by the Pesaro experience [70], the disease status at the time of transplantation, and thus the timing of HSCT, appear to be critical to outcome in TM. Indeed, the identification and the adoption, in clinical practice, of three risk classes identified on the basis of three criteria, namely, hepatomegaly, liver fibrosis, and regularity of iron chelation, have been shown to influence HSCT outcomes. [70].

The EBMT recently reported data from a retrospective study of 1493 TM patients given allo-HSCT, with the best results observed in recipients of MFD-HSCT, in whom 2-year OS and EFS probabilities were 91% and 83%, respectively, while the 2-year estimates of both OS and EFS in the MUD-HSCT subgroup were 77%. A significant threshold age of 14 years for optimal results was identified [71].

Based on these considerations, TM children with a suitable, unaffected, HLA-identical sibling should be offered HSCT at an early disease stage, before the development of treatment-related complications and/or tissue damage associated with iron overload. Unfortunately, for the majority of patients, a suitable MFD is not available, leading to the need for alternative transplantation strategies.

Thanks to the dramatic advances achieved in the field of allogeneic HSCT, outcomes after MUD-HSCT in TM now approach those obtained in the MFD setting, provided that the donor selection is performed using high-resolution molecular typing for HLA class I and II *loci* and according to strict criteria of donor/recipient compatibility (i.e., full match or single allelic disparity for HLA-A, B, C, DRB1, and DQB1 *loci*). Moreover, a significantly increased risk of graft rejection has been described in the presence of non-permissive HLA-DPB1 mismatches in the host-versus-graft (HvG) direction, with a lower probability of DFS in patients given HSCT from donors with at least one HLA-DPB1 non-permissive disparity [72].

Unrelated UCBT holds the potential to broaden the access to HSCT to patients lacking an MFD or MUD, and this procedure appears appealing in non-malignant diseases by virtue of a suggested lower risk of GVH-D. Nevertheless, discordant results have been reported in the experience with unrelated UCBT in TM, with high rates of graft failure, largely attributable to low HSC content in cord blood units (CBUs) [73]. Based on currently available experience, unrelated UCBT appears to be a suboptimal strategy in TM, unless it is performed in the context of clinical trials aimed at exploring specific treatment platforms of ex-vivo UCB graft manipulation.

Although experience with haploidentical HSCT in children with TM is limited and this type of allograft is not routinely recommended, currently explored platforms hold the potential to extend the access to HSCT to the proportion of TM patients lacking both an HLA-matched related and unrelated donor [65, 74].

Sickle Cell Disease

While transfusion dependency is currently considered an indication for HSCT in TM, a general agreement on indications and timing for HSCT in SCD is less defined.

Indications for allogeneic HSCT in SCD include: (1) stroke or central nervous system event lasting longer than 24 h, acute chest syndrome with recurrent hospitalizations or previous exchange transfusions; (2) recurrent vaso-occlusive pain (more than two episodes per year over several years) or recurrent priapism; (3) impaired neuropsychological function with abnormal cerebral magnetic resonance imaging (MRI) scan; (4) stage I or II sickle lung disease; (5) sickle nephropathy (moderate or severe proteinuria or a glomerular filtration rate 30–50% of the predicted normal value); (6) bilateral proliferative retinopathy with major visual impairment in at least one eye; (7) osteonecrosis of multiple joints; and (8) red-cell alloimmunization during long-term transfusion therapy [69].

More recently, additional risk factors have been suggested and these are being considered in the evaluation of the risk/benefit ratio for transplantation in SCD (see also Table 6.6) [75].

Table 6.6 Indications for HSCT in SCD balanced with donor availability

HLA-identical donor (BM or CB)	HLA-matched-unrelated donor or unrelated CB	HLA-haploidentical donor
– Stroke	– Recurrent stroke	– Recurrent stroke despite adequate chronic transfusion therapy and/or hydroxyurea
– Elevated TCD velocity	– Elevated TCD velocity/ worsening cerebral vasculopathy	– RBC alloimmunization in patients with indication for chronic transfusion therapy
– Recurrent acute chest syndrome	– Recurrent acute chest syndrome despite supportive care	
– Recurrent VOC	– Recurrent VOC despite supportive care	– Pulmonary hypertension
– Recurrent splenic sequestration	– RBC alloimmunization in patients with indication for chronic transfusion therapy	– Inability to tolerate supportive care though strongly indicated, e.g., RBC alloimmunization, severe VOC, and inability to tolerate hydroxyurea
– Pulmonary hypertension/ tricuspid regurgitation jet velocity > 2.5 m/s	– Pulmonary hypertension	
– Osteonecrosis/AVN		
– RBC alloimmunization		
– Silent stroke with cognitive impairment		
– Recurrent priapism		
– Sickle nephropathy		

BM bone marrow, *CB* cord blood, *TCD* transcranial Doppler, *VOC* veno-occlusive crisis, *AVN* avascular necrosis, *RBC* red blood cell, *SCD* sickle cell disease

A further aspect to mention is that donor-host hematopoietic mixed chimerism after HSCT is not a rare finding in patients with hemoglobinopathies. As documented for both TM and SCD, the development of stable mixed chimerism in non-malignant disorders maintains the potential to correct the phenotypic expression of the disease [76]. This observation has provided a rational basis for considering RIC regimens in patients with hemoglobinopathies, with the aim of promoting stable engraftment of at least a threshold fraction of donor cells, sufficient to correct the abnormal hemoglobin phenotype, while reducing toxicity.

Acquired Severe Aplastic Anemia

Acquired aplastic anemia is a disorder characterized by BM failure and peripheral blood pancytopenia, assumed to result from an immune-mediated destructive mechanism that may be triggered by environmental exposures. First-line allo-HSCT is

considered the treatment of choice if an HLA-identical sibling donor is available. For patients lacking an MFD, IST consisting of ATG, cyclosporine, and steroids is employed as frontline treatment strategy.

HSCT from a well-matched unrelated donor is currently considered a rescue option for children who have failed IST, with OS and EFS approaching 80% and 70%, respectively [77].

The results of two recently reported retrospective studies suggest a potential benefit also of upfront HSCT from unrelated donors in children affected by severe aplastic anemia (SAA) [78, 79]. In the first analysis of 29 children given frontline MUD-HSCT, outcomes were similar to those observed in a historical control group given MFD-HSCT (2-year OS: 96% in the upfront MUD-HSCT group and 91% in the MFD-HSCT group, $P = 0.30$; 2-year EFS 92% in the upfront MUD-HSCT group and 87% in the MFD-HSCT group, $P = 0.20$) and superior to IST (OS 94%, $P = 0.68$; EFS 40%, $P = 0.0001$) and MUD-HSCT post-IST failure (OS 74%, $P = 0.02$; EFS 74%, $P = 0.02$). Similar outcomes were reported in 42 children and adolescents (estimated failure-free survival rate of the frontline HSCT group 91.3% vs. 30.7% in the frontline IST group, $P < 0.001$).

Alternative options, such as UCBT [80] or haploidentical HSCT [81], may be considered in patients lacking a matched related or unrelated donor and failing IST.

Constitutional Bone Marrow Failure Syndromes

Fanconi Anemia

Fanconi anemia (FA) is a genetically and phenotypically heterogeneous disorder, variably characterized by congenital somatic abnormalities, BM failure, and predisposition to clonal disorders. HSCT currently represents the only possibility of cure, having the potential to correct the hematologic manifestations associated with FA, as well as to prevent/treat myeloid malignancies. Due to the peculiar chromosome fragility and hypersensitivity to DNA interstrand cross-linking agents that characterize this disorder, conditioning regimens that are specifically developed for FA patients are employed.

In the therapeutic decision-making process for patients with FA, multiple factors should be taken into consideration. Indeed, the risk of developing BM failure and hematologic malignancies increases with age, and a variety of factors, such as the recipient's age, extent of prior treatments, and disease stage have been shown to negatively affect the outcome of HSCT [82].

Commonly accepted absolute indications for HSCT are severe BM failure with transfusion dependence, and clonal evolution to HR MDS (i.e., RCC with HR chromosomal abnormalities or advanced MDS) or AML. Relative indications that may lead to the choice of transplantation in the presence of an MFD can also be moderate isolated cytopenias with evidence of progression towards transfusion dependence and low-risk MDS (i.e., RCC with no chromosomal abnormalities or low-risk chromosomal abnormalities).

Dyskeratosis Congenita

Dyskeratosis congenita (DC) is an inherited disorder characterized by mucocutaneous abnormalities, BM failure, and predisposition to cancer, resulting from mutations in genes involved in telomere maintenance.

HSCT represents the only chance of definitive cure for the hematologic abnormalities associated with DC, but it is, unfortunately, associated with significant early and late morbidity. As in FA, due to the underlying defect in genome maintenance, RIC protocols are required for DC. Transplantation should be performed at centers experienced in treating DC, considering the risk of graft failure and early mortality, as well as long-term complications such as diffuse vasculitis and lung fibrosis.

Diamond-Blackfan Anemia

Diamond-Blackfan anemia (DBA) is a disorder associated with mutations in genes that encode for ribosomal proteins, clinically characterized by hypo-regenerative anemia with absent or decreased BM erythroid precursors, which may be associated with somatic abnormalities. Conservative therapy in DBA includes chronic transfusions and corticosteroids. HSCT may be offered to patients who develop transfusion-dependence or other cytopenias.

Data from the Diamond-Blackfan Anemia Registry of North America and AIEOP indicate OS probabilities of 72–74% after MFD- or MUD-HSCT, and 17% after HSCT from alternative donors [83, 84].

Considering the incomplete penetrance of DBA, disease-causing mutations may be present in subjects without an evident DBA phenotype, rendering genetic analysis of any potential related donor mandatory.

Severe Congenital Neutropenias and Inherited Thrombocytopenias

The category of severe congenital neutropenias includes a variety of hematologic disorders characterized by severe neutropenia, with a high risk of developing severe and life-threatening bacterial infections from early infancy.

More than 90% of patients respond to treatment with recombinant human (rHu) granulocyte colony-stimulating factor (G-CSF), obtaining neutrophil counts higher than 1.0×10^9/L. Allogeneic HSCT remains the only currently available treatment for patients with severe congenital neutropenia (Kostmann disease) refractory to rHuG-CSF or those who develop clonal evolution into MDS or leukemia [85].

HSCT also represents the only possibility of cure in congenital amegakaryocytic thrombocytopenia (CAMT), an autosomal recessive disorder caused by mutations of the gene encoding for the thrombopoietin (TPO) receptor (c-MPL), clinically characterized by early-onset thrombocytopenia (at birth) with reduced or absent BM megakaryocytes, and eventual progression to BM failure [86].

Inborn Errors of Metabolism

Inborn errors of metabolism (IEMs) are disorders derived from the deficiency of enzymes that play a key role in metabolic pathways. The consequent progressive accumulation of toxic metabolites within different cells/tissues leads to multisystemic impairment. The observation that the enzymatic activity in deficient cells could be restored by mixing, in culture, normal cells and fibroblasts derived from patients affected by mucopolysaccharidoses, led to the first attempts at HSCT in this kind of IEM. Moreover, unlike in enzyme-replacement therapy, donor-derived monocytes are able to cross the blood-brain barrier, thus alleviating/arresting central nervous system damage.

To date, more than 2000 transplants have been performed worldwide in patients with IEMS, with results showing that not all IEMs can benefit from HSCT [87]. A possible partial explanation for this observation could lie in the fact that HSCT seems to induce a response only in some tissues, probably due to the suboptimal delivery of the target enzyme in non-responder tissues. In IEMs, the timing of transplantation appears to be critical for outcome, as late HSCT may be ineffective in preventing disease progression [88]. In particular, for patients who have already developed central nervous system involvement or those with advanced disease, HSCT is contra-indicated. The use of donors who carry the enzymatic defect is not recommended, because the delivery of the target enzyme in recipient tissues is suboptimal. The full-donor chimerism rate was found to be significantly higher in recipients of UCBT as compared with patients receiving either BM or peripheral blood transplantation.

Solid Tumors

Because of continuous improvements in multimodal therapy and supportive care, the outcomes of children with solid tumors have constantly improved in the past few decades. However, some of these tumors, although initially chemosensitive, have a dismal prognosis. Against this background, both auto- and allo-HSCT have been employed for the treatment of HR solid tumors [89], with the former strategy being the most widely used (only 446 allogeneic transplant procedures were registered at the EBMT until 2011). However, with the exception of neuroblastoma (for which randomized trials have been conducted, showing a clear advantage of auto-HSCT versus sole chemotherapy) [90], prospective trials are lacking. From registry data, the following findings can be inferred [91]:

- Outcomes of HSCT performed during first-line treatment are significantly better than those observed after transplantation in relapsed patients.
- Patients with good response at the time of transplantation (i.e., complete response, very good partial response, and partial response) have, not surprisingly, an improved outcome when compared with those with an unsatisfactory response.

– Recent years have seen a trend towards a reduction of TRM.
– Peripheral blood autologous stem cells represent the currently most often used HSC source.
– Total body irradiation has shown no advantage for any of the solid tumor indications; however, busulfan coupled with melphalan increased survival in neuroblastoma and Ewing sarcoma.

Tumors for which there is a general indication for auto- or allo-HSCT are listed in Table 6.1.

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