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SPECIAL REPORT

Allogeneic and autologous transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe 2009

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The European Group for Blood and Marrow Transplantation regularly publishes special reports on the current practice of haematopoietic SCT for haematological diseases, solid tumours and immune disorders in Europe. Major changes have occurred since the first report was published. HSCT today includes grafting with allogeneic and autologous stem cells derived from BM, peripheral blood and cord blood. With reduced-intensity conditioning regimens in allogeneic transplantation, the age limit has increased, permitting the inclusion of older patients. New indications have emerged, such as autoimmune disorders and AL amyloidosis for autologous HSCT and solid tumours, myeloproliferative syndromes and specific subgroups of lymphomas for allogeneic transplants. The introduction of alternative therapies, such as imatinib for CML, has challenged well-established indications. An updated report with revised tables and operating definitions is presented.
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Introduction

This report is the fifth report from the European Group for Blood and Marrow Transplantation (EBMT) classifying allogeneic and autologous haematopoietic SCT procedures according to prevailing clinical practice in Europe.[1–4] Since the first report, major changes have occurred in clinical practice based on new scientific and technical developments of new indications but also changed indications for HSCT based on important developments in non-transplant management of haematological malignancies. Limitations for the transplant procedures such as age and comorbidities have been modified because of the introduction of reduced-intensity conditioning regimens. The updated classifications are presented below (Tables 1 and 2). As in the previous reports, we have attempted to summarize the opinions and practices of clinicians working in transplant centres in Europe in 2008. The EBMT recommendations are based on existing prospective clinical trials, registry data and expert opinion, but not on a formal extensive review of the literature. Therefore, some recommendations have been made on the basis of analogy, inference and expertise. Each section of the recommendations has been discussed within the appropriate working party of the EBMT. The EBMT recommendations are not meant to decide for an individual patient whether a transplant is the correct choice of procedure. It is also outside the scope of this report to classify indications on the basis of the use of a particular conditioning regimen or of a particular stem cell source. The classifications are aimed to give guidance and have to be considered together with the risk of the disease, the risk of the transplant procedure and the results of non-transplant strategies. When the recommendations are interpreted, it is important, besides a possible survival

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Table 1 Proposed classification of transplant procedures for adults—2009

Disease	*Disease status*	*Sibling donor*	*Allogeneic*		*Autologous*
			Well-matched unrelated	*mm unrelated >1 Ag mm related*	
Leukaemia					
AML	CR1 (low risk[a])	CO/II	D/II	GNR/II	CO/I
	CR1 (intermediate[a])	S/II	CO/II	D/II	S/I
	CR1 (high risk[a])	S/II	S/II	CO/II	CO/I
	CR2	S/II	S/II	CO/II	CO/II
	CR3, incipient relapse	S/III	CO/III	D/III	GNR/III
	M3 molecular persistence	S/II	CO/II	GNR/III	GNR/III
	M3 molecular CR2	S/II	CO/II	GNR/III	S/II
	Relapse or refractory	CO/II	D/II	D/II	GNR
ALL	CR1 (standard/intermediate[a])	D/II	GNR/II	GNR/III	D/III
	CR1 (high risk[a])	S/II	S/II	CO/II	D/II
	CR2, incipient relapse	S/II	S/II	CO/II	GNR/II
	Relapse or refractory	CO/II	D/II	D/II	GNR/III
CML	First chronic phase (CP), failing imatinib	S/II	S/II	CO/III	D/II
	Accelerated phase or >first CP	S/II	S/II	CO/II	D/III
	Blast crisis	CO/II	CO/II	CO/II	GNR/III
Myelofibrosis	Primary or secondary with an intermediate or high Lille score	S/II	S/II	D/III	GNR/III
Myelodysplastic syndrome	RA, RAEB	S/II	S/II	CO/II	GNR/III
	RAEBt, sAML in CR1 or CR2	S/II	S/II	CO/II	CO/II
	More advanced stages	S/II	CO/II	D/III	GNR/III
CLL	Poor-risk disease	S/II	S/II	D/III	CO/II
Lymphomas					
Diffuse large B-cell lymphoma	CR1 (intermediate/high IPI at dx)	GNR/III	GNR/III	GNR/III	CO/I
	Chemosensitive relapse; ⩾CR2	CO/II	CO/II	GNR/III	S/I
	Refractory	D/II	D/II	GNR/III	GNR/II
Mantle cell lymphoma	CR1	CO/II	D/III	GNR/III	S/II
	Chemosensitive relapse; ⩾CR2	CO/II	D/II	GNR/III	S/II
	Refractory	D/II	D/II	GNR/III	GNR/II
Lymphoblastic lymphoma and Burkitt's lymphoma	CR1	CO/II	CO/II	GNR/III	CO/II
	Chemosensitive relapse; ⩾CR2	CO/II	CO/II	GNR/III	CO/II
	Refractory	D/III	D/III	GNR/III	GNR/II
Follicular B-cell NHL	CR1 (intermediate/high IPI at dx)	GNR/III	GNR/III	GNR/III	CO/I
	Chemosensitive relapse; ⩾CR2	CO/II	CO/II	D/III	S/I
	Refractory	CO/II	CO/II	D/II	GNR/II
T-cell NHL	CR1	CO/II	D/II	GNR/III	CO/II
	Chemosensitive relapse; ⩾CR2	CO/II	CO/II	GNR/III	D/II
	Refractory	D/II	D/II	GNR/III	GNR/II
Hodgkin's lymphoma	CR1	GNR/III	GNR/III	GNR/III	GNR/I
	Chemosensitive relapse; ⩾CR2	CO/II	CO/II	CO/II	S/I
	Refractory	D/II	D/II	GNR/II	CO/II
Lymphocyte predominant nodular HL	CR1	GNR/III	GNR/III	GNR/III	GNR/III
	Chemosensitive relapse; ⩾CR2	GNR/III	GNR/III	GNR/III	CO/III
	Refractory	GNR/III	GNR/III	GNR/III	CO/III
Other diseases					
Myeloma		CO/I	CO /II	GNR/III	S /I
Amyloidosis		CO/II	CO/II	GNR/III	CO/II
Severe aplastic anaemia	Newly diagnosed	S/II	CO/II	GNR/III	GNR/III
	Relapsed/refractory	S/II	S/II	CO/II	GNR/III
PNH		S/II	CO/II	CO/II	GNR/III
Breast cancer	Adjuvant high risk	GNR/III	GNR/III	GNR/III	CO/I
Breast cancer	Metastatic responding	D/II	D/II	GNR/III	D/CO/II
Germ cell tumours	Sensitive relapses	GNR/III	GNR/III	GNR/III	CO/II

Table 1 Continued

Disease	*Disease status*	*Sibling donor*	*Allogeneic*		*Autologous*
			Well-matched unrelated	*mm unrelated >1 Ag mm related*	
Germ cell tumours	Third-line refractory	GNR/III	GNR/III	GNR/III	S/I
Ovarian cancer	CR/PR	GNR/III	GNR/III	GNR/III	D/I
Ovarian cancer	Platinum-sensitive relapse	D/III	GNR/III	GNR/III	GNR/III
Medulloblastoma	Post-surgery	GNR/III	GNR/III	GNR/III	D/CO
Small-cell lung cancer	Limited	GNR/III	GNR/III	GNR/III	D/I
Renal cell carcinoma	Metastatic, cytokine-refractory	CO/II	CO/II	GNR/III	GNR/III
Soft cell sarcoma including	Metastatic, responding	D/III	GNR/III	GNR/III	D/II
Immune cytopenias		CO/II	D/III	D/III	CO/II
Systemic sclerosis		D/III	GNR/III	GNR/III	CO/II
Rheumatoid arthritis		GNR/III	GNR/III	GNR/III	CO/II
Multiple sclerosis		D/III	GNR/III	GNR/III	CO/II
SLE		D/III	GNR/III	GNR/III	CO/II
Crohn's disease		GNR/III	GNR/III	GNR/III	CO/II
CIDP		GNR/III	GNR/III	GNR/III	D/III

Abbreviations: CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; CO = clinical option; can be carried after careful assessment of risks and benefits; CR1, 2, 3 = first, second and third CR; D = developmental; further trials are needed; GNR = generally not recommended; IPI = international prognostic index; mm = mismatched; MRD = minimal residual disease; PNH = paroxysmal nocturnal haemoglobinuria; RA = refractory anaemia; RAEB = refractory anaemia with excess blasts; S = standard of care; generally indicated in suitable patients; sAML = secondary AML; SLE = systemic lupus erythematosus.
[a]Categories are based mainly on number of white blood cells, cytogenetics at diagnosis and molecular markers, and time to achieve remission according to international trials.
This classification does not cover patients for whom a syngeneic donor is available.

gain, to assess issues of quality of life and late effects into the risk assessment strategy. Such effects are especially important in children.

Definitions

Haematopoietic SCT

HSCT refers to any procedure where haematopoietic stem cells of any donor type and any source are given to a recipient with the intention of repopulating and replacing the haematopoietic system in total or in part. Stem cells can be derived from BM, peripheral blood or cord blood (CB). For allogeneic HSCT, repopulation can be measured by determining chimerism in the peripheral blood and/or BM. The goal of the procedure should be defined beforehand and a documented informed consent of the patient (and donor) obtained before the procedure.

Donor categories

Donor type is categorized as autologous, syngeneic, HLA-identical sibling donor, other family donor or unrelated donor. A well-matched unrelated donor is defined as a 9/10 or 10/10 identical donor based on HLA high-resolution typing for class I (HLA-A, -B, -C) and II (HLA-DRB1, -DQB1). Allelic-matched unrelated BM donor 10/10 transplants have been compared with HLA-identical sibling HSCT and give similar outcomes.[5] A mismatched unrelated donor is defined as a 6–8/10 matched donor based on the above definition or a less than 8/8 match (not including DQB1.[6] A haploidentical donor is defined as a full HLA haplotype-mismatched family member. A good collaboration with the HLA typing laboratory is essential for the selection of the best available donor.

Donor lymphocyte infusions

Donor lymphocyte infusions are defined as the infusion of lymphocytes (or subsets) obtained from the HSCT donor of an allogeneic HSCT with the aim to enhance engraftment, shift the balance between the donor and recipient haematopoiesis in favour of donor type, prevent rejection, treat or prevent relapse. It is not considered a second allogeneic transplant. The goal of the procedure should be defined beforehand and a documented informed consent of the patient and donor should be obtained before the procedure.

Risk factors for outcome

The main risk factors for outcome are the stage of the disease, the age of the patient, the time interval from diagnosis to transplant and, for allogeneic HSCT, the donor/recipient histocompatibility and the donor/recipient sex combination. The risk factors add up and can be quantified as illustrated in Table 3. TRM increases and survival rates decrease with advanced disease stage, increasing age, increasing time from diagnosis to transplant, increase in HLA disparities, and for male recipients having a female donor. All components should be integrated into risk assessment and decision making for a transplant. These factors are never absolute. Generally, HSCT in children gives better results than in adults but age cannot be seen as a single risk factor. It must be considered together with other factors in decision making.[7] It should, however, be recognized that biological rather than chronological age is the more important determining factor for

Table 2 Proposed classification of transplant procedures for children—2009

Disease	*Disease status*	*Sibling donor*	*Allogeneic*		*Autologous*
			Well-matched unrelated	*mm unrelated >1 Ag mm related*	
Haematological malignancies					
AML	CR1 (low risk)	GNR/II	GNR/II	GNR/III	GNR/II
	CR1 (high risk)	S/II	CO/II	GNR/III	S/II
	CR1 (very high risk)	S/II	S/II	CO/II	CO/III
	CR2	S/II	S/II	S/II	S/II
	>CR2	CO/II	D/II	D/II	GNR/II
ALL	CR1 (low risk)	GNR/II	GNR/II	GNR/III	GNR/II
	CR1 (high risk)	S/II	S/II	CO/II	GNR/II
	CR2	S/II	S/II	CO/II	CO/II
	>CR2	S/II	S/II	CO/II	CO/II
CML	Chronic phase	S/II	S/II	D/II	GNR/III
	Advanced phase	S/II	S/II	D/II	GNR/III
NHL	CR1 (low risk)	GNR/II	GNR/II	GNR/II	GNR/II
	CR2 (high risk)	CO/II	CO/II	GNR/II	CO/II
	CR2	S/II	S/II	CO/II	CO/II
Hodgkin's disease	CR1	GNR/II	GNR/II	GNR/II	GNR/II
	First relapse, CR2	CO/II	D/III	GNR/III	S/II
Myelodysplastic syndromes		S/II	S/II	D/III	GNR/III
Non-malignant diseases; solid tumours					
Primary immunodeficiencies		S/II	S/II	S/II	NA
Thalassaemia		S/II	CO/II	GNR/III	NA
Sickle cell disease (high risk)		S/II	CO/III	GNR/III	NA
Aplastic anaemia		S/II	S/II	CO/II	NA
Fanconi anaemia		S/II	S/II	CO/II	NA
Blackfan–Diamond anaemia		S/II	CO/II	GNR/III	NA
CGD		S/II	S/II	CO/III	NA
Kostman's disease		S/II	S/II	GNR/III	NA
MPS-1H Hurler		S/II	S/II	CO/II	NA
MPS-1H Hurler Scheie (severe)		GNR/III	GNR/III	GNR/III	NA
MPS-VI Maroteaux- Lamy		CO/II	CO/II	CO/II	NA
Osteopetrosis		S/II	S/II	S/II	NA
Other storage diseases		GNR/III	GNR/III	GNR/III	NA
Autoimmune diseases		GNR/II	GNR/II	GNR/II	CO/II
Germ cell tumour		GNR/II	GNR/II	GNR/II	CO/II
Ewing's sarcoma (high risk or >CR1)		D/II	GNR/III	GNR/III	S/II
Soft tissue sarcoma (high risk or >CR1		D/II	D/II	GNR/III	CO/II
Neuroblastoma (high risk)		CO/II	GNR/III	GNR/III	S/II
Neuroblastoma >CR1		CO/II D/III	D/III	S/II	
Wilms' tumour >CR1		GNR/III	GNR/III	GNR/III	CO/II
Osteogenic sarcoma		GNR/III	GNR/III	GNR/III	D/II
Brain tumours		GNR/III	GNR/III	GNR/III	CO/II

Abbreviations: CO = clinical option; can be carried out after careful assessment of risks and benefits; CR1, 2, 3 = first, second and third CR; D = developmental; further trials are needed; GNR = generally not recommended; mm = mismatched; NA = not applicable; S = standard of care; generally indicated in suitable patients.
This classification does not cover patients for whom a syngeneic donor is available.

outcome with reduced-intensity conditioning regimens in allogeneic transplantation. According to the EMEA Guidelines on Clinical Investigation of Medicinal Products, patients up to the age of 18 years are for the purpose of this document classified as children and adolescents.

Stem cell sources

Today, there are three commonly used sources of haematopoietic stem cells: BM, G-CSF mobilized PBSCs and CB stem cells. For autologous HSCT, PBSC has become the preferred choice because of a more rapid

Table 3 Quantification of risk of TRM

Disease stage	
Early (for example, AML first CR)	0
Intermediate (for example, AML second CR)	1
Advanced (for example, refractory disease)	2
Age of patient	
<20 years	0
20–40 years	1
>40 years	2
Time interval diagnosis to transplant	
<12 months	0
>12 months (does not apply for patients in first CR)	1
Histocompatibility	
HLA-identical sibling	0
Other donor	1
Gender combination	
Other	0
Female donor for male recipient	1
Additional elements	
Comorbidity/Karnofsky >80	1
Donor >50 years	1
CMV not −/−	1
Identical twin (syngeneic)	−1
Unrelated donor 10/10 high-resolution matched	−1

haematopoietic reconstitution. For allogeneic HSCT, all three stem cell sources are used and have their specific advantages and disadvantages. PBSCs are associated with more rapid engraftment but are also associated with an increased risk of chronic GVHD compared with BMT.[8] The higher risk for chronic GVHD might therefore make peripheral blood SCT a less attractive option for children, or for some patients with early stage disease. Whether paediatric donors should be considered for G-CSF mobilization and PBSC donation is also debatable. Though there may be a specific advantage in collecting PBSCs from children in the case of considerable disparity with the recipient's body weight, this practice should be discouraged in standard allogeneic transplants. Furthermore, the additional graft-versus-malignancy effect seen in patients with chronic GVHD is not applicable for patients with non-malignant conditions such as severe aplastic anaemia (SAA). BM is therefore seen as the preferred choice in these indications.[9] The donor's preferences must also be taken into account as there are differences in the side effects experienced by the donors from a BM or PBSC harvest.

Cord blood stem cells may be used in the context of HLA genotypically identical allogeneic HSCT. As this is quite a rare situation, unrelated CB cells are more commonly used when patients lack an HLA-identical sibling or a well-matched unrelated donor. An additional advantage is that CB cells can be obtained rapidly and may therefore be the best option when a patient needs an urgent HSCT. The indications for the use of CB as a source for stem cells in children are identical to the indications listed in Table 1. CB units should be selected by HLA matching and cell dose. The most important factor influencing outcome is the cell dose, and a minimum dose of $2.5–3 \times 10^7$ nucleated cells/kg at collection or 2×10^7 nucleated cells/kg at infusion is recommended. HLA disparity should not exceed two of six defined by HLA-A, -B Ag and HLA-DRB1 allele typing. Outcomes of unrelated CB HSCT in children and adults with acute leukaemias are comparable with well-matched unrelated BM transplants.[10,11] The use of double CB units is under investigation with promising results.[12,13] The requirements of cell dose and the number of HLA disparities for the double units are the same as for single units. Thus, no more than two of six HLA disparities should exist between each CB unit and the patient. The use of CB in the context of reduced-intensity conditioning HSCT is under investigation but currently follows the same recommendations as for myeloablative conditioning regimen (Eurocord, unpublished data).

Reports of haploidentical HSCT have shown promising results in patients with high-risk diseases. The use of haploidentical donors can therefore be indicated when no other donor can be found and another curative approach is not available.[14] Such procedures should be performed in specialized centres capable of managing the high risk for infectious complications because of delayed immune reconstitution. Furthermore, standardized protocols for graft processing (CD34+ selection, T-/B-cell depletion) must be used.[15] In addition, certain HLA-C and HLA-B mismatches have been observed to give rise to donor vs recipient natural killer (NK) cell alloreactivity affecting beneficially on outcome.[16–19]

Reduced-intensity conditioning regimen

Conditioning regimens vary in their intensity and can be classified as standard intensity, reduced intensity or intensified regimens. A wide variety of reduced-intensity conditioning (RIC) regimens have been described and the results clearly show that RIC-HSCT can decrease the risk for early TRM, thereby making transplants for older patients and for patients with comorbidities possible. Follow-up of RIC-HSCT shows that long-term disease control can be obtained. In many patients, an RIC-HSCT is the only alternative available as a myeloablative transplant would be associated with a very high risk of early mortality. Results have been published for related donor HSCT older than 75 years and for unrelated donor HSCT up to 70 years. The experience with unrelated donors is comparable with those with related donors. No prospective or retrospective study has, however, shown superior long-term results with RIC-HSCT compared with standard HSCT. A conventional transplant remains the therapy of choice for younger patients without comorbidities in the absence of results from prospective controlled trials. However, reports also suggest that in children the aggressive pretransplant conditioning might be replaced by milder and less toxic regimens if there are comorbidities or other contraindications for conventional transplant or for a second or subsequent transplant. RIC transplants are discouraged in patients with progressive or refractory disease.

Categorization of transplant procedures

An important aim of the EBMT indication documents has been to classify indications and to give advice about the settings where these types of transplants ought to

be performed. These have been classified as 'standard of care (S)', 'clinical option (CO)', 'developmental (D)' or 'generally not recommended (GNR)'.

Standard of care
Indications categorized as 'standard of care ' are reasonably well defined and results compare favourably (or are superior) to those of non-transplant treatment approaches. Obviously, defining an indication as the standard of care does not mean that an HSCT is necessarily the optimal therapy for a given patient in all clinical circumstances. 'Standard of care' transplants may be performed in a specialist centre with experience with HSCT procedures and an appropriate infrastructure as defined by the JACIE guidelines.

Clinical option
The 'CO' category is based on the fact that, for many indications, the number of patients will be low and therefore randomized studies comparing conventional treatment and HSCT are difficult to perform. Results of small patient cohorts treated for this disease by HSCT show efficacy and acceptable toxicities of the procedure. The broad range of available transplant techniques combined with the variation of patient factors such as age and comorbidity makes interpretation of these data difficult. Our current interpretation of existing data for indications placed in this category supports the fact that HSCT is a valuable option for individual patients after a careful discussion of risks and benefits with the patient, but that for groups of patients the value of HSCT needs further evaluation. Transplants for indications under this heading should be performed in a specialist centre with major experience with HSCT procedures, with an appropriate infrastructure as defined by EBMT guidelines and optimally meeting JACIE standards.

Developmental
Indications have been classified as developmental if there is little experience with this indication in combination with the type of transplant and when additional research is needed to define the role of HSCT. These transplants should be performed within the framework of a clinical protocol. Such a protocol can either be a randomized comparison of two or more approaches to treatment or a small pilot series undertaken by transplant units with acknowledged expertise in the management of that particular disease or that type of HSCT. Patients are therefore offered the opportunity to undergo HSCT in the context of a study that has been designed specifically to cover a series of patients who satisfy defined diagnostic criteria. The category also covers fundamentally new approaches to the management of a disease that, in a different stage, may already be classified under the standard of care or CO. Protocols for 'developmental' transplants will have been approved by local research ethics committees and must be according to current international standards. It is implied that the results of the study are intended for presentation to and/or publication for the medical community at large. Centres performing transplants under the category of 'developmental' should meet JACIE standards. The document for Rules and Regulations for EBMT Clinical Trials could also be used as a guideline (http://www.ebmt.org/1WhatisEBMT/Op_Manual/OPMAN16_Clinical%20Trials%20Guidelines.pdf).

Generally not recommended
The GNR category can include early disease stages when results of conventional treatment do not normally justify the additional risk of TRM, or when the disease is so advanced that the chance of success is so small that the risk of the harvest procedure for the normal donor is difficult to justify. 'GNR' may not apply to specific situations where a syngeneic donor exists. This category also includes HSCT for a disease in a phase or status in which patients are conventionally not treated by HSCT. Therefore, there will be some overlap between 'GNR' and 'developmental' and further research might be warranted within prospective clinical studies for some of these indications. 'GNR' does not exclude the fact that centres with a focus on a certain disease can investigate HSCT in these situations.

Data reporting
Reporting of transplant data is mandatory for EBMT members and the minimum amount of data to be reported is contained in the MED-A form. To fully assess the impact of certain transplant strategies for specific indications, reporting of data on a larger case record form (MED-B data) is encouraged. Reporting on MED-B forms should be standard practice for transplants classified as CO and developmental and especially if transplants for 'GNR' indications are performed.

Evidence grading
There has been no attempt to perform a formal evidence review as the basis for the indication classification, but a broad classification has been made as described below. In this classification, results from therapeutic strategies other than HSCT have also been taken into account.

i Evidence from at least one well-executed randomized trial;
ii Evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies (preferably from more than one centre); multiple time-series studies; or dramatic results from uncontrolled experiments;
iii Evidence from opinions of respected authorities based on clinical experience, descriptive studies or reports from expert committees.

Status of transplants in specific diseases in adults

The updated classification of HSCT procedures in adults is shown in Table 1.

AML
Adults with AML in first remission may be treated by HSCT. HSCT can be used as planned consolidation in first

CR, as rescue for patients refractory to standard induction chemotherapy, at first relapse, or in second CR. The decision depends on the risk of the disease and the risk of the transplant procedure. Allogeneic HSCT is not recommended for patients in first CR with cytogenetically 'favourable' subtypes ((t(8;21); inv(16); t(15;17)). However, in patients with acute promyelocytic leukaemia not achieving a molecular response after consolidation in frontline or after salvage treatment, an allogeneic HSCT is a CO. Patients in first CR with other cytogenetic abnormalities or normal karyotype (including those with FLT-3 mutations) are candidates for HLA-identical sibling donor HSCT. Analyses of other molecular markers as indicators of AML subsets with distinct prognosis are still under validation. Patients in first CR considered as high risk because of to specific cytogenetic abnormalities or specific molecular markers, such as FLT-3 and MLL, are candidates for an allogeneic HSCT from either an HLA-identical sibling or unrelated donor. Patients failing to achieve CR after one course of induction chemotherapy may be treated by allogeneic HSCT. Patients with advanced AML, defined as in an early relapse or in second or later remission, may also be treated by allogeneic HSCT. Patients with AML in first CR may be treated by auto-HSCT with or without purging of the graft when a suitable donor is not available. Results of HSCT for AML must be compared with results of contemporary chemotherapy regimens. Recently, promising results have been reported with unrelated CB and T-cell-depleted haploidentical HSCT for patients with AML. Those strategies are still under investigation in CR1 but should be considered for patients in CR2 lacking an HLA-identical sibling or well-matched unrelated donor. In the haploidentical setting, HSCT from donors who mount donor vs recipient NK cell alloreactivity is associated with a significantly lower relapse rate and better EFS, particularly when patients are transplanted in CR.[17–19]

ALL

Adults with ALL with poor prognostic features, for example, t(9;22) or t(4;11), or slow response to induction chemotherapy, are candidates for allogeneic HSCT from either an HLA-identical sibling or an unrelated donor. Allogeneic HSCT for standard risk patients in CR1 should be performed within a clinical protocol. Patients relapsing after chemotherapy and achieving CR2 are candidates for allogeneic HSCT from an HLA-identical sibling, an unrelated donor or other alternative donors such as CB or haploidentical donor.

CML

HSCT remains the only curative treatment for CML. However, after the advent of tyrosine kinase inhibitors (TKIs), allogeneic HSCT can rarely be recommended to chronic phase patients as first-line therapy, except in case of patient's preference or, in regions where access to TKI is limited because of economic reasons, where early HSCT may be considered in young patients with an EBMT score 0–2.

Adults with suboptimal responses to or failing imatinib according to the European Leukaemia Net guidelines should have a search for a suitable donor initiated as early as possible. Second-line therapy for patients with a donor should be based on the risk of HSCT and the likelihood of response to second generation TKI. The EBMT risk score (Gratwohl score) might be used to identify patients at low risk for TRM. The EBMT score might also be used in combination with the Sokal or Hasford score for identifying patients who could undergo HSCT with an increased risk for disease progression without HSCT.

Patients with ABL mutations that are resistant to second generation TKI may proceed directly to HCT. In patients without ABL mutations resistant to second generation TKI, the second generation TKI should be started and HSCT considered as preferential therapy at the time of best response if (a) the EBMT score is 0–2 and one of the following: additional clonal evolution, failure to achieve at least minor cytogenetic response with imatinib, high Sokal score at diagnosis or loss of haematological response to imatinib, or (b) if the EBMT score is 0–5 and there is one of the following during treatment with second generation TKI: failure or insufficient response or intolerance to or mutations resistant to second generation TKI.

Patients should proceed to HSCT, regardless of the EBMT score, if there is progression to accelerated or blast phase at presentation or during imatinib or second generation TKI therapy.

Patients in the advanced phase at diagnosis should be referred for HSCT as soon as possible. While preparing for HSCT, initial therapy with imatinib or intensive therapy ± imatinib might be an option. HSCT should be performed as soon as possible after achieving the second chronic phase.

Patients with controlled accelerated phase and blast crisis after treatment with chemotherapy and/or TKI are candidates for allogeneic HSCT from an HLA-identical sibling, an unrelated donor or other alternative donors such as CB or haploidentical family donors. A patient with a syngeneic donor is always a candidate for HSCT with standard conditioning.

Autologous HSCT should only be recommended in the context of clinical studies.

Myeloproliferative disorders other than CML

Allogeneic HSCT is today the only curative option for patients with myeloproliferative disorders. Polycythaemia vera (PV) and essential thrombocythaemia (ET) are in general not indications for allogeneic HSCT unless the disease has progressed to myelofibrosis or secondary leukaemia. Owing to the lack of alternative therapeutic options, allogeneic HSCT is a reasonable treatment for primary myelofibrosis with intermediate and high risk according to the Lille score or myelofibrosis post-ET or PV and should be considered for all patients younger than 60 years of age.[20,21] The experience of allogeneic HSCT in young patients with low-risk Lille score is limited and remains controversial. The available data do not support splenectomy before HSCT. Autologous HSCT can induce responses in patients with primary myelofibrosis,

but this procedure cannot be recommended outside clinical protocols.

MDS

Allogeneic HSCT is considered the treatment of choice for adult patients with myelodysplastic syndrome (MDS) or AML evolved from MDS and offers a good chance of long-term disease-free survival, if the treatment is performed before progression of the disease or if the patient is transplanted in CR after chemotherapy. The international prognostic score is a valuable tool to assess a patient's prognosis without HSCT. Additional prognostic factors, such as multilineage dysplasia and transfusion requirement, may be considered as well.[22] The results seem to be better in allogeneic HSCT if the blast count does not exceed 5% at the time of transplant. The practice in Europe is to treat MDS patients with excess of marrow blasts with remission induction therapy, but this approach has not been substantiated by prospective clinical trials. Treatment with azacytidine before HSCT is another option to reduce the risk for relapse. The decision to proceed with allogeneic HSCT should be based on the risk of the disease and the risk of the transplant procedure as estimated by the EBMT risk score. The results of a large European study show that autologous HSCT can be recommended in patients with good-risk cytogenetic characteristics.[23]

CLL

Allogeneic HSCT from an HLA-identical sibling or well-matched unrelated donor is a treatment option for young patients having previously been treated with and progressing after fludarabine-containing regimens and have poor-risk disease as defined by clinical and cytogenetic/molecular assessments.[24] Mature phase II studies and registry analyses have shown that allogeneic HSCT is the only therapy with proven curative potential. In contrast to conventional treatment, it can provide long-term disease control even in genetically unfavourable and refractory cases, and is clearly superior to any other salvage regimen despite an increased TRM when used with myeloablative conditioning. Autologous HSCT could be considered for patients with poor-risk disease in complete or good PR able to withstand high-dose therapy, but should preferably be performed in the context of a clinical protocol.

Hodgkin's lymphoma

Classical Hodgkin's lymphoma

Autologous HSCT is the standard therapy for patients with Hodgkin's lymphoma (HL) in first chemosensitive relapse or second CR as shown by two prospective randomized clinical trials.[25,26] There is currently no indication for autologous HSCT in first CR, even in patients with bad prognostic features at diagnosis.[27,28] Patients with disease refractory to first-line therapy but sensitive to salvage therapy might benefit from an autologous HSCT.[29] For truly primary refractory patients or for patients in chemorefractory relapse, autologous HSCT has only a small likelihood to induce long-term remission[30,31] but can be considered in some patients as other therapeutic strategies do not seem to offer better results. As part of a clinical protocol for patients with resistant Hodgkin's disease, autologous HSCT might be considered as an initial debulking therapy to be followed by an allogeneic HSCT as consolidation therapy.[32]

Allogeneic HSCT has mainly been used as salvage therapy for multiply relapsed or refractory HL patients. Allogeneic HSCT with myeloablative conditioning carries a high risk for TRM.[33,34] The use of RIC is able to significantly decrease TRM in these relapsed/refractory patients as indicated by a retrospective analysis of the EBMT.[35] A myeloablative conditioning regimen should therefore be considered only for selected young patients. The role of RIC in relapsed/refractory HL needs to be defined. Nowadays, more than 50% of the patients who undergo an RIC have previously failed an autologous HSCT.[36,37] A retrospective analysis indicates that RIC can improve the outcome of HL patients relapsing after an autologous HSCT.[38] Nevertheless, 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.[36,37]

Lymphocyte-predominant nodular HL

Lymphocyte-predominant nodular HL has to be considered a complete separate entity and there is almost no information in the literature regarding the impact of SCT in the long-term outcome of these patients. Nevertheless, autologous HSCT can be considered a therapeutic option for those patients in advanced stages and relapsing after conventional chemotherapy protocols.

Non-Hodgkin's lymphoma—adults

Diffuse large B-cell non-Hodgkin's lymphoma

Autologous HSCT is still considered the standard therapy for patients with chemosensitive relapse of diffuse large B-cell lymphoma (DLBCL) as indicated by the only phase III randomized prospective clinical trial that addresses this issue, the Parma trial.[39] Nevertheless, the exact role of autologous HSCT is being re-evaluated with the advent of monoclonal antibodies and the widespread use of chemoimmunotherapy as first-line treatment for all these patients. The role of autologous HSCT as first-line therapy in DLBCL patients with intermediate-high or high international prognostic index at diagnosis is still controversial. Although there are many phase III randomized prospective clinical trials that have analyzed this question, the design and the results of these trials are profoundly heterogeneous.[40–42] Two recent meta-analyses summarizing these studies showed heterogeneous results and no OS benefit.[43,44] Autologous HSCT is not an option for refractory patients with DLBCL. New and innovative approaches should be sought for these patients.

Patients relapsing after or resistant to first-line therapy have a very poor prognosis especially if relapse occurs <12 months after primary treatment. Such patients along with those failing multiple treatment modalities, including an

autologous HSCT, might be considered candidates for an allogeneic HSCT, although the role of such a strategy is not defined. There are no direct comparisons between the use of myeloablative conditioning and RIC. Nevertheless, more than 50% of the patients in the EBMT registry have received an RIC. Results of RIC mainly come from multicentre trials including a small number of patients, heterogeneous regarding disease status, conditioning regimen and GVHD prophylaxis and with a short follow-up.[45,46] Only prospective clinical trials including a sufficient number of patients will be able to adequately address this point.

Follicular lymphoma

Therapies for follicular lymphoma (FL) patients are changing because of the use of chemoimmunotherapy as first-line treatment, the introduction of radioimmunotherapy and the quickly evolving concept of maintenance with monoclonal antibodies. Patients with FL are normally not considered candidates for an autologous HSCT as first-line therapy, although three phase III prospective clinical trials[47–49] performed before the 'rituximab era' suggested a role in some subgroups of high-risk patients. Autologous HSCT remains the standard approach for early relapsing patients with FL.[50] New prospective trials analyzing the role of autologous HSCT in recurrent FL are needed and should include rituximab and other new modalities. Results of autologous HSCT in truly refractory patients are poor. These patients should probably be offered alternative approaches.

Allogeneic HSCT has mainly been performed in patients with multiple relapses, including a prior autologous HSCT. RIC was used in more than 50% of the cases both in the United States[51] and in Europe (EBMT registry), although there is no prospective randomized trial comparing the approaches. From the information derived from retrospective registry analyses[45] and from single centre prospective phase II trials[52] as well as multicentre prospective analyses,[45,46,53] the TRM and relapse rate are low and the long-term outcome seems favourable. The impact of the use of alternative donors (for example, MUD) in relation to HLA-sibling donors is under evaluation. Prospective studies need to be performed.

Mantle cell lymphoma

Although most patients with mantle cell lymphoma (MCL) are offered an early intensification with an autologous HSCT owing to the inherent bad prognosis of the disease, the only phase III prospective clinical trial showing the superiority of an autologous HSCT was published before the introduction of anti-CD20 monoclonal antibodies.[54] Most of the information on autologous HSCT as first-line therapy in MCL comes from phase II prospective trials. Autologous HSCT is considered standard therapy for patients with MCL relapsing after a first-line treatment. Nevertheless, information from retrospective analysis indicates that the results of autologous HSCT beyond first CR are inferior. Autologous HSCT does not provide any clinical benefit in patients with refractory disease.

Suitable patients with relapsed disease after an adequate first-line therapy could be considered candidates for an allogeneic HSCT despite the fact that data are only available from very small phase II clinical trials and retrospective registry analyses. Therefore, allo-HSCT should be considered an experimental procedure.

T-cell lymphomas

Peripheral T-cell non-Hodgkin's lymphomas (PTL) usually have a very poor prognosis. Results exist from phase II trials[55] and multicentre retrospective analyses, suggesting a positive effect of autologous HSCT. These patients should be included in prospective clinical trials. Phase II prospective trials[56] and retrospective studies[57] indicate the potential benefit of RIC allogeneic HSCT in patients with a PTL in second response. There is almost no information on allo-HSCT as early consolidation therapy for patients with PTL.

Burkitt's lymphoma, lymphoblastic lymphoma

Little information exists regarding the impact of HSCT in both Burkitt's lymphoma and lymphoblastic lymphoma patients. Patients with lymphoblastic lymphomas can be consolidated with an autologous HSCT in first CR, as indicated by some phase II trials.[58] Allogeneic HSCT can eventually be considered in young adults in first CR.[59] Burkitt's lymphoma patients with bad prognostic features at diagnosis can also be consolidated with an autologous HSCT.[58] Allogeneic HSCT can be considered for patients in CR2.

Myeloma

Autologous HSCT is clearly indicated for patients <70 years of age who respond to first-line treatment. Age should be considered in conjunction with the patient's general health and fitness. New agents such as the proteasome inhibitors (bortezomib) or the immunomodulating agents, such as lenalidomide, may change the place of autologous HSCT. Best results are seen in patients achieving good responses before HSCT, but some non-responding patients also benefit from this approach. Double autologous HSCTs have been shown to be superior to one autologous HSCT, although the benefit of the second transplant seems to be restricted to patients not achieving CR or very good PR with the first transplant; consolidation and maintenance with agents such as thalidomide may be an alternative for these patients. However, the vast majority of patients still relapse. The use of a further transplant after reinduction therapy is an option and may be of particular benefit in patients achieving a long treatment-free interval after their first transplant(s). TBI should not be used in the conditioning regimen owing to increased toxicity without appreciable benefit. Allogeneic HSCT is a treatment with curative potential, but it is associated with considerable TRM and might be used in selected high-risk patients. The results of the combination of auto HSCT followed by RIC-HSCT are inconsistent. One study reported a superior outcome compared with double autologous HSCT[60] and a second study shows a trend for better outcome.[61] However, two other studies have so far not shown any benefit. However,

longer follow-up is needed. The combination of auto HSCT and unrelated RIC-HSCT is currently being investigated.

AL amyloidosis
Patients with AL (amyloid in systemic Ig-light-chain) amyloidosis have been treated by autologous HSCT. A study with matched controls showed that amyloidosis patients without severe heart failure benefited from high-dose therapy and auto-HSCT, but this was not confirmed in a recently published study.[62] Allogeneic HSCT might be considered as a CO in patients with progressive disease.

Acquired severe aplastic anaemia adults
Allogeneic BMT from an HLA-identical sibling is the treatment of choice in patients with SAA under the age of 30. The choice in patients between 30 and 45 years of age is more difficult, and both BMT and immunosuppression give good results. In older patients, or in the absence of an HLA-matched sibling, an initial course of a combination of ATG and CYA should be given. The median time for response after this treatment is 2–3 months. One should therefore wait at least 4 months for assessment of response before a transplant is undertaken, especially if it is from an unrelated donor. The conditioning regimen for sibling transplants should not include irradiation because of the high risk of secondary tumours. Unrelated donor and mismatched family donor transplants are still associated with significant morbidity but are the standard of care when other therapies have failed.

Constitutional SAA, including Fanconi anaemia
Allogeneic HSCT is the only curative treatment for patients with constitutional SAA. For patients lacking an HLA-identical sibling donor, transplantation from an unrelated donor may be considered. The conditioning regimen should preferably not include radiation, and the dosage of the chemotherapy is to be reduced as appropriate for patients with Fanconi anaemia.

Paroxysmal nocturnal haemoglobinuria
Small numbers of patients with paroxysmal nocturnal haemoglobinuria have been treated with allogeneic HSCT, which seems to be the only curative approach. Therefore, an allogeneic HSCT is a CO for patients with high-risk disease who have a well-matched donor.

Solid tumours—adults
The existence of a dose-response effect in epithelial tumours (breast, ovarian, small cell lung cancer) is still a matter of investigation. However, the benefit of high-dose chemotherapy (HDCT) in selected subgroups of patients has become clearer. The role of autologous HSCT for primary breast cancer at high risk of recurrence (at least four involved axillary lymph nodes) has been assessed in a meta-analysis of individual patient data from 15 known randomized trials comparing HDCT with standard-dose chemotherapy.[63] It was shown that HDCT prolonged disease-free survival when used as adjuvant therapy, and showed a benefit on breast cancer-specific survival and OS. Whether HDCT has benefit in the context of contemporary taxane-based regimens and targeted therapies is unknown. In the context of metastatic breast cancer, HDCT seems to be effective in stage IV patients rendered free of macroscopic disease by previous therapy and in patients with oligometastatic disease.

High-dose chemotherapy for germ cell tumours is considered a CO for sensitive relapse and as standard therapy for refractory disease. A tandem transplant comprising high-dose carboplatin and high-dose etoposide followed by an infusion of autologous PBSC should be considered the standard of care as third-line or later therapy or in patients with platinum-refractory disease, excluding primary mediastinal disease.[64] Conversely, data do not support the use of HDCT as first-line treatment in patients with metastatic germ cell tumour and poor prognostic clinical features.[65]

A randomized phase III study for first-line treatment of advanced ovarian cancer in which high-dose sequential chemotherapy with PBSC support was compared with standard-dose chemotherapy was published. No statistically significant difference in progression-free survival or OS was observed.[66] Small-cell lung cancer (SCLC) is a chemosensitive tumour. A randomized phase III trial in patients with limited or extensive SCLC compared conventional-dose vs HDCT. No difference in the median progression-free survival and OS was noted among the two arms.[67] Some limitations of the study may have accounted for the lack of favourable results.

Allogeneic HSCT is considered a CO for renal cancer relapsed/resistant to cytokine therapy, a developmental therapy for breast and ovarian cancer, that is not recommended for other solid tumours with the possible exception of colorectal cancer. The number of allogeneic HSCTs has decreased in recent years. The reasons for this decrease have been: (i) the introduction in clinical trials of molecularly targeted agents, especially for renal cancer, (ii) the lack of well-designed phase II studies, (iii) the high TRM owing to accrual of rapidly progressing, high tumour burden patients. Attempts to improve the therapeutic index of allogeneic HSCT in solid tumours by innovative clinical strategies are underway. Currently, allogeneic HSCT should only be considered in the context of prospective clinical trials.

Autoimmune disorders—adults
Autologous HSCT after appropriate conditioning to maximize immunosuppression is being considered in clinical protocols for selected patients with severe multiple sclerosis,[68] rheumatoid arthritis,[69] systemic lupus erythromatosus,[70] systemic sclerosis,[71] immune cytopenias and Crohn's disease.[72] Autologous HSCT for other autoimmune disorders is being considered on a developmental basis. Dependency of high steroid doses above the 'Cushing threshold' and causing skeletal damage could be an indication. Allogeneic HSCT is being considered on a developmental basis in patients selected for very poor prognosis.

Status of transplants in specific diseases in children and adolescents (Table 2)

AML

In paediatric AML, the role of allo-HSCT in CR1 is declining because of the better outcome with modern multiagent chemotherapy. Hence, HSCT is not recommended as frontline therapy for good-risk patients with AML.[73] Allogeneic HSCT from an HLA-identical sibling in CR1 remains an option for children defined as high risk as it was proven to be more efficient than chemotherapy in some comparative studies, with vent-EFS ranging from 55 to 72%. Infant AML and children with FAB M0, M6 or M7 AML, who stand very poor chances of cure by chemotherapy or by autologous HSCT, are indications for unrelated donor HSCT. Results in children with AML undergoing haploidentical HSCT have shown some effect of NK alloreactivity, suggesting that haploidentical HSCT may have a role in early phase very high-risk AML patients.[74]

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 paediatric studies comparing autologous HSCT with chemotherapy are conflicting. The use of PBSCs 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.[75]

In children with relapsed AML, allogeneic HSCT is indicated either from a sibling or an unrelated donor.

ALL

The indication for HSCT in children with ALL in CR1 is limited to the subpopulation of high-risk ALL. Most study groups define these patients as having estimated an EFS of $<50\%$. The risk factors indicating the usefulness of HSCT are known molecular biological markers or chromosomal abnormalities, biological factors including poor prednisone response, and resistance to initial chemotherapy including persistence of minimal residual disease.[76] For these patients, allogeneic HSCT from matched sibling donors or a well-matched unrelated donor, and for the highest risk category a mismatched donor is also an option.[77]

ALL patients, who experience an early marrow relapse, still have a dismal prognosis when treated with conventional chemotherapy. Although nearly 90% achieve a second remission, most of them subsequently develop progressive disease. Both matched sibling donor HSCT and unrelated donor HSCT are clearly indicated in these patients as the outcomes are similar.[78,79] If a matched sibling or a well-matched unrelated donor cannot be identified, other types of donors such as CB, mismatched unrelated donors or haploidentical family donors, particularly when they exert NK alloreactivity, can be indicated.[19,80] The indication for autologous transplantation is limited to a small subset of patients with either a late BM or an extramedullary relapse.[81]

CML

CML is a rare disease in children. Since the approval of TKI also for children and adolescents, HSCT is no longer the first treatment for patients with early phase CML. However, as lifelong medication with TKI is necessary, there are treatment failures and continuous contraception is mandatory. HSCT still remains an important treatment option, especially for younger patients with CML depending on national, physician and patient preferences. HSCT might be postponed for patients achieving a haematological response at 3 months, followed by a minor cytogenetic response at 6 months and followed by a complete cytogenetic response at 12 months after start of imatinib at a dose of $300\,mg/m^2$. Once imatinib refractoriness develops, patients should undergo HSCT. However, prospective cooperative studies are needed to address this complex issue in young patients with CML.

Malignant lymphoma

Children suffering from lymphomas have a good prognosis when treated with first-line chemo- and radiotherapy. Patients,who fail to respond or those with chemosensitive recurrent diseases can achieve long-term disease-free survival after autologous HSCT. The impact of allogeneic HSCT in children with lymphomas has not been clarified. Allogeneic HSCT in children and adolescents with recurring lymphomas may be beneficial, especially in children with a good performance status and available matched donor; this strategy should be carefully considered at an early time point in children failing standardized primary and salvage treatment.

MDS

Allogeneic HSCT from a sibling donor or a well-matched unrelated donor is the treatment of choice for children with primary MDS, including juvenile myelomonocytic leukaemia, and secondary AML. The role of autologous HSCT in children with MDS remains controversial and is GNR.

Inherited diseases: primary immunodeficiencies

Primary immunodeficiencies are inherited disorders characterized by impairment of innate or adoptive immunity, commonly leading to lethal complications. Allogeneic HSCT can cure most of the lethal forms of immunodeficiencies, including SCIDs, several T-cell immunodeficiencies, Wiskott-Aldrich syndrome, phagocyte disorders such as leukocyte adhesion deficiency and chronic granulomatous diseases, haemophagocytic syndromes such as familial lymphohistiocytosis, Chediak-Higashi syndrome, Griscelli's disease and X-linked lymphoproliferative syndrome. Treatment by HSCT is increasingly successful. Owing to the clinical heterogeneity of the patients, the several existing variants for each primary immunodeficiency associated with the need to carefully evaluate the patient's clinical conditions, and the fact that drugs are used in different dosages, combinations and time schedules according to the disease, the age and the clinical condition of the patient,

HSCT for primary immunodeficiency should be performed in a centre regularly performing such transplants and that actively participates within EBMT's inherited diseases working party. The guidelines for each particular inherited condition are published on the EBMT's website and reviewed regularly by the Inherited Disease working party members. Allogeneic HSCT is indicated for severe primary immunodeficiencies from both HLA-identical and alternative donors.

SCID
A patient with SCID needs to be grafted as soon as possible. An allogeneic HSCT results in a survival rate of more than 90% when carried out shortly after birth. Prognostic factors are the age, the type of SCID (B(+) vs B(−)), the clinical state at the time of diagnosis, in particular the presence of a lung infection, and the degree of HLA histocompatibility. In the presence of an HLA-identical family donor (20–30% of SCID patients), HSCT can be performed in certain SCID forms without any conditioning regimen and its course is characterized by the remarkable rarity of acute and chronic GVHD without any prophylaxis and by the rapid development of the T-cell function after transplant. The restoration of the B-cell function nearly always occurs in patients with the B(+) form of SCID, but is absent in 40% of those with a B(−) form. In the absence of an HLA-identical family donor, HSCT from a partially HLA-compatible donor is proposed. In this respect, the use of a conditioning regimen has a positive effect on survival in the B(−) SCID group but not in the other SCID groups. HSCT from unrelated HLA-compatible donors, and unrelated umbilical CB and haploidentical HSCT from related donors (that is, one of the two parents) are alternative options.

Inherited diseases: metabolic diseases

Most of the metabolic diseases are lysosomal storage diseases that rely on transfer of enzyme from donor-derived blood cells to the reticuloendothelial system and solid organs. The success of the HSCT can be affected by the lack of engraftment (secondary rejection is comparatively common), the enzyme levels of the donor, the degree of sustained donor chimerism and possibly by the immune processes directed against the normal donor enzyme. In disease with the central nervous system involvement, amelioration is dependent on the replacement of microglial cells by cells of donor origin. This process is slow and the time taken to process abnormal storage material produces a delay between transplant and disease stabilization. This can last up to 15 months, making it necessary to best guess how the quality of life will be 18 months on from first consideration of HSCT (allowing for a donor search, workup and conditioning).

Aplastic anaemia, pure red cell aplasia (Blackfan-Diamond) and Fanconi anaemia—children
An allogeneic HSCT with an HLA-identical family donor is the treatment of choice for children with acquired SAA. A course of intensive immunosuppressive therapy (ATG and CYA) is indicated for patients who lack an HLA-compatible family donor. The search for an unrelated donor should be initiated while they receive the immunosuppressive therapy. For children who fail their first course of immunosuppression, if a well-matched unrelated donor is identified, the transplant or a second course of immunosuppression should be given according to the clinical status. Children with Blackfan–Diamond anaemia having a matched sibling should be transplanted if they do not respond to steroids or if they do not become independent of these drugs. Children with Fanconi anaemia shall be transplanted if they have an HLA-identical sibling donor or a well-matched unrelated donor. For patients who lack a well-matched donor, HSCT should be considered with a mismatched unrelated donor or with CB stem cells in the context of a clinical protocol.

Haemoglobinopathies—children
The outcome of HSCT for thalassaemia has progressively improved with identification of the Pesaro classes of risk and the development of new conditioning regimens and supportive therapies. Allogeneic HSCT from a healthy related sibling donor or a related CB represents the treatment of choice for young patients with homozygous thalassaemia. For patients who lack a sibling donor, a transplant from a well-matched unrelated donor is a possibility. Extended haplotype matching seems to have a positive impact on prognosis after unrelated donor HSCT. Developments of conventional therapy have improved both the quality and the duration of life for patients with sickle cell disease. For this reason, HSCT from an HLA-identical sibling is offered only to a subset of patients at high, life-threatening risk or to patients who cannot receive adequate support. The experience of well-matched unrelated donor HSCT for sickle cell disease is still very limited and additional studies are needed.

Solid tumours—children
Neuroblastoma (stage IV beyond the age of 1 year, or high-risk factors in lower stages) is still the only indication where the benefit of high-dose therapy with autologous HSCT has been shown by randomized trials.[82,83] Although to date the published results do not show an unequivocal benefit for consolidation with high-dose therapy, children and adolescents with solid tumours might undergo autologous HSCT after high-dose chemotherapy within clinical research trials, preferably as part of first-line treatment strategies in the following situations:

- Neuroblastoma (high risk, >CR1).
- Ewing's sarcoma (high risk or >CR1).
- Brain tumours: 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 tumours: after a relapse or with progressive disease.
- Wilms' tumour: relapse.
- Osteogenic sarcoma: the value of HSCT is not yet clear.

- Generally, allogeneic HSCT cannot be recommended in children with solid tumours. Allogeneic HSCT may be undertaken in the context of a clinical protocol in specialized centres.

Autoimmune disorders
Selected patients with poor prognostic juvenile idiopathic arthritis are currently considered for autologous HSCT that has been proven as effective in providing a prolonged drug-free remission in a significant percentage of patients.[84] Other diseases can be considered as developmental. The dependency of high steroid doses and impaired growth could be an indication.

Allogeneic HSCT with reduced conditioning in children
For patients otherwise not treatable (for example, severe infections, heavy burden of chemotherapy, second transplants) allogeneic HSCT with reduced or minimal conditioning may be carried out within prospective clinical protocols. Developmental protocols, in particular indications (for example, solid tumours), may be undertaken as pilot protocols in specialized centres.

Conflict of interest

The authors declare no conflict of interest.

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