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SPECIAL REPORT

Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2015

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This is the sixth special report that the European Society for Blood and Marrow Transplantation regularly publishes on the current practice and indications for haematopoietic SCT for haematological diseases, solid tumours and immune disorders in Europe. Major changes have occurred in the field of haematopoietic SCT over the last years. Cord blood units as well as haploidentical donors have been increasingly used as stem cell sources for allo-SCT, thus, augmenting the possibility of finding a suitable donor for a patient. Continuous refinement of conditioning strategies has also expanded not only the number of potential indications but also has permitted consideration of older patients or those with co-morbidity for a transplant. There is accumulating evidence of the role of haematopoietic SCT in non-haematological disorders such as autoimmune diseases. On the other hand, the advent of new drugs and very effective targeted therapy has challenged the role of SCT in some instances or at least, modified its position in the treatment armamentarium of a given patient. An updated report with revised tables and operating definitions is presented.

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INTRODUCTION

This report is the sixth report from the European Society for Blood and Marrow Transplantation (EBMT) classifying allogeneic and autologous haematopoietic SCT (HSCT) procedures according to prevailing clinical practice in Europe.[1–5] Since the first report, major changes have occurred in clinical practice based on new scientific and technical developments. This includes the recognition of new indications but also changed indications for HSCT based on important developments in results of HSCT in non-haematological malignancies, including autoimmune diseases, and on novel non-transplant treatment strategies of haematological and non-haematological malignancies. New strategies based on cord blood stem cells (CB) or haploidentical donors have significantly expanded the accessibility of allo-SCT (allo-HSCT) approaches. Limitations for the transplant procedures such as age and co-morbidities have been modified because of the introduction of reduced-intensity conditioning (RIC) regimens. The updated proposed indications are presented in Tables 1 and 2. As in the previous reports, we have attempted to summarize the opinions and practice of clinicians working in transplant centres in Europe in 2015. 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 based upon 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 based on the use of a particular conditioning regimen or 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 gain, to assess issues of quality of life and late effects into the risk assessment strategy. Such effects are especially important in children and adolescents.

DEFINITIONS

Haematopoietic stem cell transplant (HSCT)

HSCT refers to any procedure where haematopoietic stem cells of any donor type and any source are given to a recipient with the

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Table 1. Proposed classification of transplant procedures for adults—2015

Disease	*Disease status*	*Sibling donor allo-HSCT*	*Well-matched URD allo-HSCT*	*Alternative donor allo-HSCT*	*ASCT*
Leukaemias					
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	CO/II	D/II	GNR/III
ALL	Ph (−), CR1 (standard risk)[a]	D/II	GNR/II	GNR/III	CO/III
	Ph (−), CR1 (high risk)[a]	S/II	S/II	CO/II	GNR/III
	Ph (+), CR1	S/II	S/II	CO/II	CO/III
	CR2, incipient relapse	S/II	S/II	CO/II	GNR/II
	Relapse or refractory	CO/II	D/II	D/II	GNR/III
CML	1st CP, failing TKI	S/II	S/II	CO/III	GNR/II
	Accelerated phase or > 1st CP	S/II	S/II	CO/II	D/III
	Blast crisis	S/II	S/II	CO/II	GNR/III
Myelofibrosis	Primary or secondary with an intermediate or high DIPSS score	S/II	S/II	S/III	GNR/III
MDS	RA, RCMD, RAEB I and II	S/II	S/II	S/II	GNR/III
	sAML in CR1 or CR2	S/II	S/II	S/II	CO/II
	More advanced stages	S/II	S/II	S/II	GNR/III
CLL	Poor risk disease	S/II	S/II	D/III	GNR/I
Lymphoid malignancies					
DLBCL	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
	Chemosensitive relapse after auto-HSCT failure	S/II	S/II	CO/III	GNR/III
	Refractory disease	CO/II	CO/II	D/III	CO/II
MCL	CR1	D/III	D/III	GNR/III	S/I
	CR/PR > 1, prior auto-HSCT no	CO/III	CO/III	D/III	S/II
	CR/PR > 1, prior auto-HSCT yes	S/II	S/II	CO/III	GNR/II
	Refractory	CO/II	CO/II	D/III	GNR/II
FL	CR1	GNR/III	GNR/III	GNR/III	D/II
	Chemosensitive relapse, ⩾CR2	CO/III	CO/III	GNR/III	S/II
	⩾CR2 after auto-HSCT failure	S/II	S/II	D/III	GNR/III
	Refractory	CO/II	CO/II	CO/III	GNR/III
WM	CR1	GNR/III	GNR/III	GNR/III	D/II
	Chemosensitive relapse, ⩾CR2	GNR/III	GNR/III	GNR/III	CO/II
	Poor risk disease	CO/II	CO/II	D/III	GNR/III
TCL	CR1	CO/II	CO/II	GNR/III	CO/II
	Chemosensitive relapse, ⩾CR2	S/II	S/II	CO/III	CO/II
	Refractory	CO/II	CO/II	CO/III	GNR/II
Primary CTCL	EORTC/ISCL Stages I–IIA (Early)	GNR/III	GNR/III	GNR/III	GNR/III
	EORTC/ISCL Stages IIB–IV (Advanced)	CO/III	CO/III	D/III	GNR/III
HL	CR1	GNR/III	GNR/III	GNR/III	GNR/I
	Chemosensitive relapse, no prior auto-HSCT	D/III	D/III	GNR/III	S/I
	Chemosensitive relapse, prior auto-HSCT	S/II	S/II	CO/III	CO/III
	Refractory	D/II	D/II	D/III	CO/III
MM		CO/I	CO/II	GNR/III	S/I
AL		CO/III	CO/III	GNR/III	CO/II
Other diseases					
Acquired SAA	Newly diagnosed	S/II	S (children)/II; CO (adults) /II	GNR/III	NA
	Relapse/Refractory	S/II	S/II	CO/II	NA
Acquired AA/PNH	Newly diagnosed	S/II	CO/II	GNR/III	NA
	Relapse/Refractory	S/II	S/II	CO/II	NA
Haemolytic PNH		GNR/II	GNR/II	GNR/II	NA
Constitutional SAA	Fanconi anaemia	S/II	S/II	CO/II	NA
	Dyskeratosis congenital	S/II	S/II	CO/II	NA
Breast cancer	Adjuvant high risk, HER2-negative	GNR/III	GNR/III	GNR/III	CO/II
	Metastatic, chemosensitive	D/II	D/II	GNR/III	D/CO/II
Germ cell tumours	Second line, high risk	GNR/III	GNR/III	GNR/III	CO/II
	Primary refractory, second & further relapse	GNR/III	GNR/III	GNR/III	S/II

Table 1. (Continued)

Disease	*Disease status*	*Sibling donor allo-HSCT*	*Well-matched URD allo-HSCT*	*Alternative donor allo-HSCT*	*ASCT*
Ovarian cancer	High risk/recurrent	D/II	GNR/III	GNR/III	GNR/I-II
Medulloblastoma	Post-surgery, high risk	GNR/III	GNR/III	GNR/III	D/CO/III
Small cell lung cancer	Limited	GNR/III	GNR/III	GNR/III	D/I-II
Soft tissue sarcoma	Metastatic	D/III	GNR/III	GNR/III	GNR/II
Ewing's sarcoma family of tumours	Locally advanced/metastatic, chemosensitive	D/III	GNR/III	GNR/III	CO/III
Renal cell carcinoma	Metastatic, cytokine-refractory	D/II	D/II	GNR/III	GNR/III
Pancreatic cancer	Advanced	D/III	GNR/III	GNR/III	GNR/III
Colorectal cancer	Metastatic	D/III	GNR/III	GNR/III	GNR/III
Multiple sclerosis		D/III	GNR/III		CO/II
Systemic scleroderma		D/III	GNR/III		CO/II
Systemic lupus erythematosus		D/III	GNR/III		CO/II
Crohn's disease		GNR/III	GNR/III		CO/II
Rheumatoid arthritits		GNR/III	GNR/III		CO/II
Vasculitis		GNR/III	GNR/III		CO/II
Polymyositis-dermatomyositis		GNR/III	GNR/III		CO/II
CIPD		GNR/III	GNR/III		CO/II
NMO		GNR/III	GNR/III		CO/II
Cytopenias		CO/II	CO/II		CO/II
T1D		GNR/III	GNR/III		D/III
RCD type II		GNR/III	GNR/III		D/III

Abbreviations: AA = aplastic anaemia; AL = amyloidosis; CLL, chronic lymphocytic; CO = clinical option, can be carried after careful assessment of risks and benefits; CP = chronic phase; CR1, 2, 3 = first, second, third CR; CTCL = cutaneous T-cell lymphoma; D = developmental, further trials are needed; DIPSS = Dynamic international prognostic score system; DLBCL = diffuse large B cell lymphoma; FL = follicular lymphoma; GNR = generally not recommended; HL = Hodgkin lymphoma; IPI = International prognostic index; M3 = Promyelocytic leukaemia; MCL = mantle cell lymphoma; MM = multiple myeloma; PNH = paroxismal nocturnal haemoglobinuria; PR, partial remission; RA = refractory anaemia; RAEB = refractory anaemia with excess blasts; RCMD = refractory cytopenia with multilineage dysplasia; S = standard of care generally indicated in suitable patients; SAA = severe aplastic anaemia; sAML = secondary AML; TCL = T-cell lymphoma; TKI = tyrosine kinase inhibitors; WM = Waldenstrom macroglobulinaemia. This classification does not cover patients for whom a syngeneic donor is available. Alternative donors denote MMUD, Cord Blood, Haploidentical Transplants. Well-matched unrelated donor = 10/10, 8/8, 9/10 (if mismatch in DQB1). [a]Categories are based mainly on number of WBCs, cytogenetics at diagnosis and molecular markers, and time to achieve remission according to international trials.[247]

intention of repopulating and replacing the haematopoietic system in total or in part. Stem cells can be derived from BM, PB or CB. 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 (MUD) is defined as a 10/10 or 8/8 identical donor based on HLA high-resolution typing for class I (HLA-A, -B, -C) and II (HLA-DRB1, -DQB1). A mis-matched unrelated donor (MMUD) refers to an adult unrelated donor mismatched in at least one Ag or allele at HLA-A, -B, -C or –DR.[6] There is growing evidence that not all HLA mismatches are created equal. Permissive HLA mismatches seem to confer similar transplant-related outcomes when compared with matched donor sources, presumably reflecting the inability of the T cell to recognize an intrinsic HLA sequence difference.[7] A non-permissive HLA allele mismatch combination leads to a poorer outcome.[8–10] MUD transplants increase donor availability but take time to organize because of donor screening and graft retrieval.

A haploidentical donor is defined as a family member where only one HLA haplotype is genetically identical with the patient. The advantages of transplantation from a haploidentical donor include the availability for almost all patients, choice of best donor from a panel of candidate family members, no undue delay in obtaining the graft and easy access to donor-derived cellular therapies if needed after the SCT procedure. Major drawbacks used to be the very strong graft-vs-host and host-vs-graft alloresponses[11] with a high incidence of severe GVHD and graft rejection after the HSCT. From the 1980s onwards, attempts to overcome the HLA barrier focused on strengthening myeloablation and immunosuppression in the conditioning regimen[12,13] or on partially depleting the graft of T cells using anti-thymocyte globulin or the T10B9 monoclonal Ab in conjunction with *in vivo* immunotoxin[14] and with post-transplantation CY and steroids. A major advance came with strategies comprising myeloablative conditioning based on TBI followed by transplantation of a mega-dose of extensively T-cell-depleted mobilized PBSC. This ensured a high engraftment rate in the absence of GVHD and has given similarly good results in both children and adults with high-risk acute leukaemia than MUD HSCT.[15–19] In recent years, interest in T-cell-replete full haplotype-mismatched HSCT was reawakened by new strategies for GVHD prophylaxis. The use of high-dose post-transplantation CY to prevent graft rejection and GVHD after nonmyeloablative conditioning and T-cell-replete BM transplantation has been extensively pioneered by the Baltimore and Seattle groups and has given promising results in terms of PFS and OS in particular in patients with lymphoid malignancies with acceptable rates of graft failure, GVHD and non-relapse mortality (NRM).[20–22]

International registries often lack complete information on HLA typing reports of unrelated donor transplants. To understand the impact of incomplete HLA characterization, the Center for International Blood and Marrow Transplant Research (CIBMTR)[23] analysed 14 797 unrelated donor HSCT (1995–2006) using multivariable regression modelling adjusting for factors affecting survival and identified three groups with significantly different outcomes; well-matched cases had either no identified HLA mismatch and informative data at 4 loci or allele matching at HLA-A, -B and -DRB1, partially matched pairs had a defined, single-locus mismatch and/or missing HLA data, and mismatched cases had $\geqslant 2$ allele or Ag mismatches. Multivariate 5-year survival estimates were significantly different for the previously established groups of patients and the authors suggested that these

Table 2. Proposed classification of transplant procedures for children—2015

Disease	*Disease status*	*Sibling donor allo-HSCT*	*Well-matched URD allo-HSCT/CBT*	*Alternative donor allo-HSCT*	*ASCT*
Haematological malignancies					
AML	CR1 (low risk[a])	GNR/II	GNR/II	GNR/III	GNR/II
	CR1 (high risk[a])	S/II	CO/II	CO/III	CO/II
	CR1 (very high risk[a])	S/II	S/II	CO/II	CO/III
	CR2	S/II	S/II	S/II	CO/II
	>CR2	S/II	CO/II	CO/II	GNR/II
ALL	CR1 (low risk[a])	GNR/II	GNR/II	GNR/III	GNR/II
	CR1 (high risk[a])	S/II	S/II	CO/II	GNR/II
	CR2	S/II	S/II	CO/II	GNR/II
	>CR2	S/II	S/II	CO/II	GNR/II
CML	Chronic Phase	CO/II	CO/II	CO/II	GNR/III
	Advanced Phase	CO/II	CO/II	CO/II	GNR/III
NHL	CR1 (low risk)	GNR/II	GNR/II	GNR/II	GNR/II
	CR1 (high risk)	CO/II	CO/II	CO/II	CO/II
	CR2	S/II	S/II	CO/II	CO/II
HL	CR1	GNR/II	GNR/II	GNR/II	GNR/II
	1st relapse, CD2	CO/II	CO/III	CO/III	S/II
MDS		S/II	S/II	CO/III	GNR/III

Disease	*Sibling donor allo-HSCT*	*Well-matched URD allo-HSCT /CBT*	*Alternative donor allo-HSCT*	*ASCT*
Non-malignant disorders; solid tumours				
Primary immunodeficiencies	S/II	S/II	S/II	NA
Thalassemia	S/II	CO/II	CO/III	NA
Sickle cell disease (high risk)	S/II	CO/III	CO/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	S/II	CO/III	NA
Chronic granulomatous disease	S/II	S/II	CO/III	NA
Kostman's disease	S/II	S/II	CO/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	CO/II	CO/II	GNR/II	CO/II
Germ cell tumour	CO/II	CO/II	CO/II	CO/II
Ewing's sarcoma (high risk or >CR1)	D/II	D/III	D/III	S/II
Soft tissue sarcoma (high risk or >CR1)	D/II	D/II	D/III	CO/II
Neuroblastoma (high risk)	CO/II	D/III	D/III	S/II
Neuroblastoma >CR1	CO/II	D/III	D/III	S/II
Wilm's 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: CBT = cord blood transplant; CO = clinical option, can be carried after careful assessment of risks and benefits; CR1, 2 = First, second CR; D = Developmental, further trials are needed; GNR = Generally not recommended; HL = Hodgkin lymphoma, generally indicated in suitable patients; MDS = Myelodisplastic syndrome; MPS = Mucopolysaccaridosis; NHL = Non Hodgkin lymphoma. Well-Matched Unrelated Donor = 10/10, 8/8. 9/10 (if mismatch in DQB1). This classification does not cover patients for whom a syngeneic donor is available. [a]Categories are based mainly on number of WBCs, cytogenetics at diagnosis and molecular markers, and time to achieve remission according to international trials.

proposed HLA sub-groupings could be used when complete HLA typing was not available. Furthermore, this improved categorization of HLA matching status could standardize interpretations of prior unrelated donor HSCT experience. This classification should only be used for retrospective analysis purposes but not to prospectively classify the degree of mismatching between a given donor and patient.

Stem cell sources

There are three commonly used sources of haematopoietic stem cells: BM, cytokine-mobilized PB progenitor cells (PBSC), and CB cells.

For autologous HSCT (auto-HSCT), PBSC is the preferred choice because of a more rapid haematopoietic reconstitution. In cases of insufficient mobilization with G-CSF-based regimens, in many patients, an adequate harvest can be achieved with the use of inhibitors of the interaction between CX chemokine receptor 4 (CXCR4) and stromal derived factor-1 alpha (SDF-1), such as plerixafor.[24–26] For allo-HSCT, all three stem cell sources are used and have their specific advantages and disadvantages. PBSCs are associated with more rapid engraftment but are associated also with an increased risk of chronic GVHD compared with BM.[27] The higher risk for chronic GVHD might therefore make PB HSCT a less attractive option for children, or for some patients with early stage disease. In some countries, it is prohibited to give G-CSF to donors who are <18 years old. Furthermore, the additional graft-vs-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 SAA when using ATG-based conditioning regimens.[28,29] 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.

Unrelated CB cells are commonly used when patients lack an HLA-identical sibling or a MUD. An additional advantage is that CB cells can be obtained rapidly and may therefore be a better 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 2 for MUD transplants. 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 $2.5–3\times10^7$ nucleated cells/kg body weight of recipient at collection or 2×10^7 nucleated cells/kg at infusion is recommended; a higher dose of $>4\times10^7$ nucleated cells/kg is needed for SAA patients. HLA disparity should not exceed two of six defined by HLA-A, -B Ag and HLA-DRB1 allele typing. According to registry analyses, outcomes of unrelated CB HSCT in children and adults with acute leukaemia are comparable with MUD BM transplants.[30,31] In adults with relapsed/refractory lymphoproliferative disorders, unrelated CB HSCT achieves comparable outcomes than those of RIC unrelated HSCT.[32]

To overcome the cell-dose limitation, Barker *et al*.[33] pioneered the use of double cord blood transplant, sequentially infusing 2 CB units instead of 1. The results were encouraging, with all patients engrafting neutrophils in a median of 23 days (range, 15–41). The requirements of cell dose and 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. Interestingly, the incidence of acute GVHD seems to be higher after double cord blood transplant although this fact does not impact on NRM[34] and the relapse rate is lower[35] in comparison with a single unit cord blood transplant. A registry analysis suggested that in patients with acute leukaemia being allografted with a myeloablative conditioning regimen, double cord blood transplant seems to be a associated to a lower relapse rate in comparison with matched related donors, MUD and 1-Ag MMUD although NRM is higher, thus rendering no significant differences in terms of leukaemia-free survival (LFS), supporting the use of two partially HLA-matched CB units when patients lack an HLA-matched donor.[36] Several single centre and retrospective analysis support the use of RIC regimens in the setting of cord blood transplant.[37–40]

Combined transplantation of a single CB unit with CD34+ stem cells from a HLA-mismatched auxiliary donor (haplo-cord) reliably reduces the time to neutrophil engraftment, in comparison with other CB strategies, to approximately day +12.[41–43] In addition, haplo-cord provides comparable overall outcomes to other donor sources while allowing the use of single CB units with relatively low cell content, and expands donor availability reducing CB cell dose requirements.

Nowadays, and with a patient being a potential candidate for an allo-HSCT who lacks a HLA well-matched donor (HLA identical sibling/MUD), physicians are faced with the need to select amongst different options: MMUD, CB or haploidentical transplants. Despite the large number of phase II and observational studies, the dearth of randomized trials makes the prioritization of an alternative donor difficult and the decision may in part reflect the research agenda of the transplantation centre because no one source of stem cells is clearly superior to another. If a donor is urgently required, CB and haploidentical transplantation have the advantage over adult volunteer MMUD. If upfront costs are a concern, haploidentical family members have a clear advantage over CB and MMUD. For patients with prior infectious problems, CB may be the less desirable stem cell source because of the delayed haematopoietic recovery and immune reconstitution. Finally, not all mismatches in the MMUD setting are equal.

Reduced intensity conditioning (RIC) regimens

The hypothesis that graft-vs-tumour effects are capable of eradicating malignant disorders led to the development of RIC regimens that made allo-HSCT an accessible therapeutic option for older and medically infirm patients who previously were not considered candidates for high-dose conditioning. Not even nowadays, has full consensus on how to define a RIC regimen been achieved by the HSCT community. The EBMT definition considers that any regimen with 50% or less equivalence to a standard conditioning regimen is considered reduced intensity. This includes not only the 50% reduction of the total dose of a given drug (or TBI), but also the use of a single drug in a standard dose but without other drugs (or TBI) usually included in the standard protocol (http://www.ebmt.org/Contents/Data-Management/Registrystructure/MEDABdatacollectionforms/Documents/MED-ABFormsManual.pdf). RIC regimens are being increasingly used in the last years and represent more than 70% of all transplantation procedures in some disease categories. Most of these regimens have been evaluated in phase 1 or 2 trials only, but there is a paucity of randomized phase 3 trials in the field.

Retrospective registry-based studies comparing myeloablative conditioning protocols with RIC regimens[44–46] indicate that the latter are associated with a lower NRM but with a higher relapse rate after the procedure thus, not significantly modifying long-term outcome of these patients both in terms of PFS and OS. In children with AML, NRM, relapse rate, PFS and OS were not significantly different between myeloablative protocols and RIC regimens.[47] In refractory/relapsed Hodgkin lymphoma (HL), children and adolescents had a better PFS because of a higher relapse rate after a RIC-allo that was not accompanied by a higher NRM in the myeloablative setting.[48] A randomized prospective clinical trial performed in young patients with AML in first remission[49] indicates that RIC regimens result in a similar incidence of NRM and reduced toxic effects compared with standard conditioning without affecting survival outcomes, and thus could be preferentially used in this setting. The role of reduced intensity is yet to be defined in the younger population of patients and additional prospective clinical trials are needed.

RISK FACTORS FOR OUTCOME

The initial analysis performed by Gratwohl[50] indicated that the main risk factors for outcome after HSCT were the stage of the disease, the age of the patient, the time interval from diagnosis to transplant and, for allo-HSCT, the donor/recipient histocompatibility and the donor/recipient sex combination (EBMT score). NRM 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 the risk assessment and the decision making for a transplant. In the case of transplant for non-malignant diseases, such as for autoimmune disorders, NRM and PFS were shown to vary according to original diseases, centre activity and conditioning.[51–53] More recently and with the development of non-myeloablative regimens and improvements in the supportive care after myeloablative protocols, more patients with co-morbidities are being offered allo-HSCT. Investigators from the Fred Hutchinson Cancer Research Center in Seattle developed the HSCT-specific co-morbidity index (HCT—CI) that integrates chronic medical conditions, which are important in predicting NRM in HSCT patients, thus producing a new scoring system that also assesses survival probabilities after allo-HSCT.[54] Further refinement of this HCT-CI indicates that Karnofsky status at transplantation is an independent prognostic factor,[55] that HCT-CI is predictive of survival across different haematological malignancies[56–58] and that, as expected, age is a poor prognostic factor with a bigger negative impact in those patients with higher HCT-CI.[59] Patients without co-morbidities usually tolerate non-myeloablative and myeloablative conditioning regimens equally well, whereas those with co-morbidities (whether young or old) have better survival after RIC protocols. The calculation of the transplantation-associated risk in a given patient is of capital importance nowadays taking into

consideration the fair competition existing between a potentially curative but more toxic treatment approach (for example, HSCT) and a non-curative but less toxic and better-tolerated strategy (for example, targeted therapy).

THE IMPACT OF A QUALITY SYSTEM ON THE OUTCOME OF HSCT

JACIE (Joint Accreditation Committee of ISCT Europe and EBMT) was started in Europe at the end of the 1990s. JACIE pursues improving the outcome of HSCT by doing it within a standardized and approved quality management system. There is increasing evidence that adherence to standardized quality management policies within an accredited program improves the outcome of allo-HSCT.[60,61]

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', 'clinical option', 'developmental' or 'generally not recommended'.

Standard of care (S)

Indications categorised 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 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 (CO)

The Clinical Option (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 co-morbidity makes interpretation of these data difficult. Our current interpretation of existing data for indications placed in this category supports HSCT as a valuable option for individual patients after careful discussions of risks and benefits with the patient but the value of HSCT needs further evaluation for groups of patients. 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 JACIE guidelines.

Developmental (D)

Indications have been classified as developmental if there is limited 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 done 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. 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 clinical option. Protocols for 'developmental' transplants will have been approved by local research ethics committees and must comply with current international standards. Rare indications where formal clinical trials are not possible should be performed within the framework of a structured registry analysis, ideally an EBMT non-interventional/observational study. 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 (GNR)

The GNR category can include early disease stages when results of conventional treatment do not normally justify the additional risk of NRM, 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 D, and further research might be warranted within prospective clinical studies for some of these indications. GNR does not exclude 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.

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 other therapeutic strategies than HSCT have also been taken into account.

1. Evidence from at least one well-executed randomized trial
2. 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
3. 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.

Acute myeloid leukaemia (AML)

Adult patients with AML should always be considered for a HSCT, either allo-HSCT or auto-HSCT. Progress has been made with the two modalities in the recent years so that previous guidelines necessitate updating. Patients with good prognosis AML by cytogenetics/molecular markers such as patients with core binding factor leukaemia (t(8;21), inv(16) or t(16;16)), patients with mono- and even biallelic gene mutation in the CCAAT/enhancer binding protein α gene (CEBPA), and patients with mutation in NPM1 but no FIT3ITTD for whom any transplant in first CR (CR1) was previously not recommended should now be

evaluated for consolidation with an auto-HSCT in CR1 if in molecular remission with no marker detectable in the leukapheresis products; or for an allogeneic transplant with an HLA identical sibling but not with an alternative donor. These recommendations come from numerous reports, including studies of the EBMT,[62] and the meta-analysis of several randomized studies[63] on 2983 patients analysed for CEBPA mutational status, which showed that relapse-free survival was significantly superior in patients receiving an allo-HSCT or an auto-HSCT in CR1 as compared with chemotherapy ($P < 0.001$), with a trend for a better OS ($P < 0.12$). As confirmation is still needed, auto- and allo-HSCT with a genoidentical donor in these patients is at present a CO, awaiting classification as standard of care.

Patients in CR1 but clinically slow responders (needing more than one course of induction to achieve CR1, or as a surrogate marker an interval from diagnosis greater than 40 days), and/or with other poor prognosis indicators such as M5 or M6 by FAB classification, poor cytogenetics defined as a complex karyotype (more than three abnormalities) or monosomy 7, inv(3)(q21q26), t(6;11)(q27;q23), t(6;9)(p23;q34) or t(11;19)(q23;p13.1)[64] and/or those with the FLT3ITD or MLL molecular mutation, should be allografted with the best available donor including genoidentical family members, unrelated donors, CB and haploidentical donors, as part of a standard of care approach; auto-HSCT is not recommended.

All other patients in CR1 with other cytogenetic abnormalities or normal karyotype belonging to the intermediate risk category are candidates for all kinds of HSCT from a well HLA-matched related or unrelated donor. Auto-HSCT has recently regained interest, thanks to several improvements such as reduced NRM with the introduction of IV BU in the pre-transplant regimen,[65] better monitoring of MRD by immunophenotyping[66] and molecular biology such as WT1 overexpression[67] and, possibly, with the introduction of maintenance therapy post autologous transplantation.[68] Analyses of other molecular markers as indicators of AML subsets with distinct prognosis are increasingly being used for decision purposes, but are still under validation.[69,70] At the present time, some therapeutic trials evaluate risk-adapted and MRD-directed transplant strategies where MRD-negative patients are autografted and MRD-positive patients allografted. In these patients, allo-HSCT is standard of care and auto-HSCT remains a clinical option waiting for further assessment. However, although there are considerable data showing better outcome of allo-HSCT with genoidentical donors over auto-HSCT, there are no such data when comparing auto-HSCT to allogeneic transplantation with alternative donors. In addition to that, the quality of life is better after an autologous than an allogeneic transplant.[71] Therefore, in MRD-negative patients, auto-HSCT is a clinical option while waiting for results of randomized studies, to possibly reach an upgrade in the categorization of transplant procedure. A recent retrospective study from CIBMTR[72] has concluded that in the absence of a matched sibling donor, auto-HSCT may provide an acceptable alternative post-remission therapy for patients with AML in CR1.

Patients with AML 3 achieving CR2 and MRD negativity should be autografted (S), because the outcome is similar or better than after allogeneic transplantation.[73–75]

Acute lymphoid leukaemia (ALL)

The field of HSCT in adult ALL remains controversial. The introduction of more aggressive chemotherapy regimens from the models developed in children to adolescents and young adults has reduced the need for allogeneic transplantation in most patients younger than 35 years of age. In contrast, allo-HSCT remains the standard of care in high-risk patients such as slow remitters or steroid and/or chemotherapy-resistant patients, patients over 35 years of age and all patients following relapse post CR1. Regarding standard risk patients, a recent randomized study comparing the outcome of 433 adult ALL patients, according to a sibling donor vs no-donor comparison has resulted in a LFS at 5 years significantly better in the donor group: 60 vs 42% (hazard ratio: 0.60; $P = 0.01$).[76,77]

In a large EBMT retrospective study performed in 2003[78] on a total of 1402 patients allografted from 1990 to 2000 with a genoidentical donor, it was possible to identify three prognostic groups based on three prognostic factors: age (below and over 35 years), response to induction (rapid and slow remitters) and donor sex. Group 1 (good prognosis) included patients aged < 35 years old, achieving CR1 with one induction course and to be transplanted with any other sex combination than female to male (score 0), group 2 (intermediate) with one adverse factor (score 1) and group 3 (bad prognosis) with two or three adverse criteria (scores 2 and 3). The 3-year LFS was 56%, 48% and 29% and the OS was 65%, 53% and 29%, respectively. Some recent studies have readdressed the question of auto-HSCT: for instance, a meta-analysis using data from 13 studies including 2962 patients,[79] excluding Philadelphia chromosome-positive (Ph pos) patients, showed a survival benefit for those patients having a matched sibling donor and for patients younger than 35 years of age (OR = 0.79, $P = 0.0003$) but not for older ones (OR = 1.01, $P = 0.9$) because of the higher absolute risk of NRM for older patients. No beneficial effect of autografting was seen compared with chemotherapy in this analysis.

In this context, the place of autologous transplant is difficult to assess. In patients over the age of 55, a very recent retrospective EBMT study (Giebel S, personal communication) on 267 patients treated with a RIC-allo and 179 patients autografted in CR1, showed better results for auto-HSCT, with a probability of OS at 2 years of 44% for RIC-allo and 57% for auto-HSCT ($P = 0.02$), owing to a significantly reduced NRM for auto-HSCT (23% vs 11%, respectively, $P = 0.002$).

In Ph pos patients, a recent EBMT retrospective study[80] indicates that results of auto-HSCT have significantly improved over time: the probability of OS at 3 years increased from 16% for transplants performed between 1996 and 2001 to 48% between 2002 and 2006 and 57% between 2007 and 2010 ($P < 0.0001$); LFS was 11%, 39% and 52%, respectively ($P < 0.0001$). Relapse incidence decreased from 70 to 45% and 45% ($P = 0.01$), respectively, while NRM was 19%, 15% and 3% ($P = 0.08$). In a multivariate analysis, year of auto-HSCT was the only independent factor influencing the risk of treatment failure (hazard ratio = 0.37; $P < 0.001$). In a subgroup of 22 patients treated with tyrosine kinase inhibitors (TKI) and being in complete molecular remission at the time of the autologous transplant, the LFS rate at 3 years was 65%. Data have been accumulated over time indicating that auto-HSCT at the time of MRD negativity obtained with the contribution of TKI is associated with good outcomes.

Adults with ALL with persistent or relapsing MRD are candidates for allo-HSCT in CR1 from either an HLA-identical sibling or an unrelated donor. Allo-HSCT for standard risk patients in CR1 should be performed whenever possible within a clinical protocol. Patients relapsing after chemotherapy and achieving CR2 are candidates for allo-HSCT from an HLA-identical sibling, an unrelated donor or other alternative donors such as CB or haploidentical donor. For patients with either Ph pos or Ph negative (Ph neg) ALL with negative MRD status, auto-HSCT is a clinical option. The role of maintenance therapy post autologous transplant remains unknown despite old favourable reports.[81]

Chronic myeloid leukaemia (CML)

HSCT remains the only curative treatment for CML. However, after the advent of TKI, allo-HSCT cannot be recommended to all patients with a suitable donor as first-line treatment after diagnosis. Imatinib should be the first-line therapy for all patients

in chronic phase. Some patients in molecular remission after treatment with imatinib have remained in molecular remission for a median of 24 months after cessation of the drug.[82] Patients with suboptimal response or failure to first-line therapy according to the European Leukaemia Net (ELN) guidelines should start a search for a suitable donor as early as possible (sibling or unrelated). They should receive treatment with second line TKI and are candidates to proceed to HSCT in optimal response as soon as possible if their EBMT risk score is 0–1 or in case of a prior loss of cytogenetic or haematological response to imatinib if their EBMT risk score is 0–4. If there is no haematological response to second line treatment, patients are candidates for allo-HSCT on any EBMT risk score (these patients may benefit from treatment with third line TKI prior to HSCT depending on ABL mutation analysis). Patients with ABL mutations known to be resistant to second generation TKI are candidates to undergo HSCT if their EBMT risk score is 0–4 after failing imatinib.

Patients in advanced phase referred for a HSCT could have therapy with TKI or intensive therapy ± TKI as preparation for HSCT. HSCT should be performed as soon as possible after achieving second chronic phase without the need to achieve deep cytogenetic or molecular responses. Patients in second chronic phase are candidates for allo-HSCT from an HLA-identical sibling, an unrelated donor, or other alternative donors such as CB or haploidentical family donor. A patient with a syngeneic donor is always a candidate for a HSCT with standard conditioning. Auto-HSCT should only be recommended in the context of clinical studies.

Myeloproliferative disorders other than CML

Allo-HSCT is today the only curative option for patients with myeloproliferative disorders. Polycythaemia vera and essential thrombocythaemia are, in general, not indications for allo-HSCT unless the disease has progressed to myelofibrosis or secondary leukaemia.[83]

Owing to the lack of alternative therapeutic options, allo-HSCT is a reasonable treatment for primary myelofibrosis with intermediate II and high risk according to the Dynamic International Prognostic Index (DIPSS). Myelofibrosis post-essential thrombocythaemia or -polycythaemia vera and should also be considered an indication for allo-HSCT for all patients younger than 65 years of age.[84] In younger patients, transplantation in intermediate I is justified in individual cases. The experience of allo-HSCT with low-risk DIPSS is limited and remains controversial. The available data do not support splenectomy prior to HSCT. The introduction of JAK inhibitors in the treatment of myelofibrosis may help to improve constitutional symptoms and to reduce spleen size before transplantation. Auto-HSCT is not recommended and should be performed only in a clinical trial.

Myelodysplastic syndromes (MDS)

Allo-HSCT is considered the treatment of choice for adult patients with 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 System (IPSS) 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.[85] The results seem to be better in allo-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, but has not yet been proven. The decision to proceed with allo-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 auto-HSCT can be recommended in patients with good-risk cytogenetic characteristics.[86]

Chronic lymphocytic leukaemia (CLL)

Allo-HSCT from an HLA-identical sibling or MUD 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.[87] Mature phase-II studies and registry analyses have shown that allo-HSCT is the only therapy with 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 chemotherapy.[88] The promising new class of BTK, PI3K and BCL2 inhibitors may be considered as treatment alternative in patients who are at high risk of treatment-related mortality.

Lymphomas

Diffuse large B-cell lymphoma (DLBCL). Auto-HSCT remains the standard of care for patients with chemosensitive relapse of DLBCL in the rituximab era.[89–91] With regard to the value of auto-HSCT as consolidation after rituximab-containing first-line therapy of DLBCL, a survival benefit for HSCT could not be shown in several randomized phase-III trials.[91,92] Therefore, upfront autologous HSCT cannot be considered as treatment standard in DLBCL. Auto-HSCT is less effective in patients with chemorefractory DLBCL but can result in long-term survival in a significant minority of them.[93]

Patients who relapse after auto-HSCT for DLBCL have only limited effective treatment perspectives. Although the available evidence is largely based on registry studies, it appears that allo-HSCT can provide long-term disease control in up to 40% of patients with DLBCL who have failed auto-HSCT, in particular if performed in chemosensitive disease.[94,95] Accordingly, allo-HSCT should be considered as a rescue option in eligible patients with this condition.[91] This notion is supported by a phase-II prospective study.[96] The value of allogeneic in comparison with auto-HSCT in high-risk relapse or refractory status of DLBCL needs to be defined by further studies.

Follicular lymphoma (FL). Although in the rituximab era still not proven by a prospective randomized trial, auto-HSCT is considered as standard treatment option in patients who are in first or subsequent relapse of FL.[91,97] In contrast, prospective phase-III trials from the pre-rituximab as well as from the rituximab era have failed to show a survival benefit of consolidating auto-HSCT performed in first FL remission,[98] implying that upfront auto-HSCT in FL should be performed only within the framework of a prospective clinical trial.[91,97] Results of auto-HSCT in truly refractory FL are poor. These patients should be offered alternative approaches. Long-term follow-up of retrospective studies of auto-HSCT for relapsed FL concordantly show that disease recurrence becomes increasingly infrequent after 6–8 years of follow-up, indicating that auto-HSCT could have curative potential in a subset of patients with FL.[99] Disease control after auto-HSCT might be further improved by rituximab maintenance as shown in a randomized phase-III clinical trial.[100]

FL generally appears to be highly sensitive to graft-vs-lymphoma effects, translating into a pronounced efficacy of allo-HSCT in terms of relapse prevention in this disease.[101,102] However, owing to the good efficacy of first-line immunochemotherapy and in the absence of valid predictors of adverse outcome, there is no place for allo-HSCT in FL in first remission. Similarly, investigators tend to prefer immunochemotherapy with or without auto-HSCT for second-line treatment of FL.

A prospective trial randomizing autologous vs allo-HSCT in this condition had to be closed prematurely because of slow accrual.[103] Supported by evidence from several retrospective uncontrolled studies, allo-HSCT therefore is reserved as a potentially curative option for those patients who have failed auto-HSCT or multiple therapy lines, or who have become refractory.[91,97,104]

Waldenström's macroglobulinaemia (lymphoplasmacytic lymphoma with IgM gammopathy) (WM). Small retrospective studies and a large registry analysis suggested that auto-HSCT might improve the outcome of WM when applied as first-line consolidation.[105,106] With the event of more effective agents, such as rituximab, purine analogues and bortezomib, this approach is increasingly questionable and should not be followed outside of clinical trials. In contrast, auto-HSCT is an option for salvage therapy in selected patients with chemosensitive disease who have not been exposed to numerous treatment lines.[106,107] There is circumstantial evidence (effects of DLI and chronic GVHD, plateau in the relapse curves, efficacy in refractory disease) from registry studies that graft-vs-lymphoma is effective in WM.[108,109] Thus, allo-HSCT has been advocated as a treatment option for younger individuals with aggressive clinical course.[110] Although a clear definition of high-risk WM is missing, indications for allo-HSCT might be considered along the criteria for poor-risk CLL (purine analogue refractoriness and relapsed disease with TP53 lesion).[87]

Mantle cell lymphoma (MCL). Auto-HSCT consolidation is considered as standard part of first-line treatment of younger ($<$60–65 years) patients with MCL.[93] This is based on several uncontrolled studies and one prospective randomized trial comparing auto-HSCT consolidation with IFN maintenance in patients with MCL in first remission.[111] This trial demonstrated that auto-HSCT provides a significant PFS benefit, and—after longer follow-up—also an OS benefit over IFN.[112] The results of upfront auto-HSCT in MCL can be further improved by incorporation of rituximab and high-dose ara-C into the induction regimen as observed in prospective randomized trials and cohort studies.[113,114] A registry analysis suggested that the benefit of auto-HSCT may also be relevant in fit elderly patients (65–70 years).[115] The prognosis of patients with relapsed or refractory MCL relapse is generally poor. Although the results of salvage auto-HSCT are inferior to first-line transplants, auto-HSCT remains a rescue option for transplant-naïve patients.[93,116,117]

Although merely supported by retrospective studies, in the absence of reasonable alternative treatment options, allo-HSCT seems to be the only modality capable of providing long-term disease control in patients with relapsed and even refractory MCL.[117,118] Therefore, it is consensus to recommend allo-HSCT to patients with MCL who relapse or become refractory after auto-HSCT or an appropriately intensive pre-treatment.[93] In contrast, there is no evidence to support upfront allo-HSCT in MCL outside of clinical trials. It remains to be shown whether novel molecular drugs, such as B cell receptor kinase inhibitors, will affect HSCT indications in MCL or other B cell malignancies in the future.[119]

T-cell lymphomas. Peripheral T-cell lymphomas usually carry a very poor prognosis. On the basis of results from phase II trials and registry analyses, auto-HSCT as consolidation of a first response represents a reasonable treatment option,[120–122] whereas its role in the relapse setting is less clear. It might be best supported in chemosensitive ALCL-type peripheral T-cell lymphomas without prior autologous transplantation.[123] The value of allo-HSCT as first-line consolidation in peripheral T-cell lymphoma is still under investigation. In contrast, phase II trials and registry analyses strongly support the notion that allo-HSCT is effective in relapsed and refractory peripheral T-cell lymphoma and the only curative modality in this condition.[122–126]

Mycosis fungoides (MF) and Sézary syndrome are the most common forms of primary cutaneous T-cell lymphomas.[127] Although early stage MF has an excellent outcome, patients with EORTC/ISCL stages IIB to IV MF and Sézary syndrome have a dismal prognosis with conventional therapy, with median survivals of only 1–3 years from the time of diagnosis.[128–130] Auto-HSCT can induce cutaneous T-cell lymphoma responses in these patients, but they are almost universally very short-lived, with median time to progression of 2–3 months, and therefore it is generally not recommended as a therapeutic strategy.[131] Conversely, allo-HSCT offers patients with advanced-stage MF and Sézary syndrome a clinically relevant and persistent graft-vs-MF/Sézary syndrome effect, leading to OS rates of 54% at 3 years, 46% at 5 years and 44% at 7 years,[132,133] which despite the lack of well-designed comparative trials, would suggest this to be an advantageous and potentially curative option for these patients compared with their outcomes with only conventional therapy.

Hodgkin lymphoma (HL). Auto-HSCT is the standard therapy for patients with HL in first chemosensitive relapse or refractory to first-line therapy but sensitive to salvage therapy as shown by two prospective clinical trials.[134,135] In contrast, there is no evidence supporting auto-HSCT in first CR. For truly primary refractory patients, for patients in chemo-refractory relapse, and for those who relapse after a previous auto-HSCT, a second one has a limited likelihood to induce durable remission, but it may be an option in patients ineligible for allo-HSCT.[136,137]

Prospective phase II trials as well as retrospective cohort comparisons and registry analyses suggest that allo-HSCT can prolong survival in comparison with the limited non-transplant options in patients who fail autologous HSCT but respond to salvage therapy.[136,138,139] Accordingly, allo-HSCT can be considered as the standard treatment option in eligible patients with sensitive relapse after auto-HSCT.[140] The value of allo-HSCT is less established in refractory HL, but may be considered in the absence of effective treatment alternatives.[141]

Multiple myeloma (MM)

Auto-HSCT is clearly indicated for patients less than 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 immunomodulatory drugs such as lenalidomide (IMiDs) may change the place of auto-HSCT. Ongoing studies are comparing induction with a combination of new agents, such as proteasome inhibitor with IMiDs, followed by upfront auto-HSCT vs delayed transplantation. Therefore, the role of first-line auto-HSCT may be challenged in the future. Best results are seen in patients achieving good responses prior to HSCT but some non-responding patients also benefit from this approach. High activity shown by IMiDs and bortezomib before transplantation has recently led to their use as consolidation and maintenance therapies after auto-HSCT. Maintenance therapy with lenalidomide post auto-HSCT may be considered. Two studies demonstrated an improvement in PFS[142,143] but an increase in OS in only one study.[143] Double auto-HSCT has been shown to be superior to one auto-HSCT although the benefit of the second transplant appears 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 re-induction therapy is an option and may be of particular benefit in patients achieving a long treatment-free interval after their first transplant(s) (at least 18–24 months).[144]

TBI should not be used in the conditioning regimen because of increased toxicity without appreciable benefit.

Allo-HSCT is a treatment with curative potential, but is associated with considerable NRM and might be used in selected high-risk patients. The results of the combination of auto-HSCT followed by RIC-allo are inconsistent. Two studies with long-term follow-up of patients treated upfront reported a superior outcome compared with single or double auto-HSCT.[145,146] and a third study shows a trend for better outcome.[147] However, three other studies with shorter follow-up have so far not shown any benefit. Longer follow-up is needed. Some phase II studies of relapsed patients show encouraging results and one that retrospectively compared HSCT and RIC-allo based on the availability of a matched donor showed better PFS with RIC-allo, however, with no difference at 2 years in OS.[148] The combination of auto-HSCT and unrelated RIC-allo is currently being investigated. Similarly to the autologous transplantation setting, new agents are complementary, non-redundant therapies and should be combined in the management of suitable allogeneic patients.

AL amyloidosis

Patients with systemic immunoglobulin-light-chain (AL) amyloidosis have been treated by auto-HSCT since 1994. A study with matched controls showed that amyloidosis patients without severe heart failure benefited from high dose therapy and auto-HSCT. This was not confirmed in a randomized trial including patients with advanced cardiac amyloidosis.[149] Many recently published studies reported an improved early mortality and consistently good haematologic responses.

Allo-HSCT might be considered as a clinical option in younger patients who relapsed or did not respond after HSCT and received at least one new drug (lenalidomide or bortezomib).

Acquired severe aplastic anaemia (SAA)

First-line allogeneic HLA identical sibling HSCT is considered for young and adult patients with SAA who have a matched sibling donor.[150–152] EBMT data show that outcomes of patients aged 30–40 years and 40–50 years are the same. However, a careful assessment of co-morbidities prior to HSCT should be made to determine fitness for up-front HSCT in the age group of 35–50 years, instead of first-line immunosuppressive therapy (IST) with ATG (preferably with horse ATG) and CYA; it is also advised to seek further advice from an AA specialist centre.

Patients transplanted from matched sibling donors and aged < 30 years should receive conditioning with high dose CY (200 mg/kg), and for patients aged 30–50 years a fludarabine-based regimen with lower dose CY (120 mg/kg) used.[153] All patients should also receive *in vivo* T-cell depletion with ATG, or alemtuzumab if available, because this will decrease the likelihood of developing chronic GVHD. There is no indication for using radiation in the conditioning for HLA identical sibling HSCT.

Allogeneic unrelated HSCT using a well-matched donor is indicated after failure to respond to one course of IST. A fludarabine-based regimen is recommended.[154] Assessment of response to IST is usually made at 3–6 months. BM is the recommended stem cell source for HSCT in SAA from sibling or unrelated donor HSCT for ATG-based conditioning regimens.[28,153,155,156] Studies are ongoing to determine whether there is any preferred stem cell source for alemtuzumab-based conditioning.

Alternative donor HSCT, using either CB cells[157,158] or a haploidentical family donor[159,160] or a mismatch 9/10 donor, may be considered in the absence of a matched sibling or unrelated donor after failure to respond to IST. All patients should be screened for donor-directed HLA antibodies as their presence would preclude using that donor because of a predicted high risk of graft rejection. For cord blood transplant, a minimum of 4×10^7/kg total nucleated cells (frozen) is recommended. The current EBMT AAWP approved protocol for either CB or haploidentical HSCT should be followed.

Paroxysmal nocturnal haemoglobinuria (PNH)

The indications for HSCT in PNH have changed since the introduction of C5 blocking monoclonal Ab therapy with eculizumab. The current indications for HSCT depend on the individual clinical manifestations of PNH, and are (i) AA/PNH syndrome, that is, PNH occurring in the presence of severe BM failure with a hypocellular BM (using the same factors of age, disease severity, and for UD HSCT failure to respond to one course of IST) and (ii) clonal evolution of PNH to MDS/AML.[152,161,162] Severe recurrent thrombosis is no longer a mandatory indication for HSCT, but can be taken into consideration when discussing the patient's treatment strategy and it may also be an option in patients who have poor haematological response to eculizumab (that is, remaining severely transfusion-dependent regardless of anti-complement treatment). HSCT is not indicated for recurrent haemolytic crises, except for patients in countries that cannot afford eculizumab treatment. If needed, expert advice should be sought from a PNH specialist centre. The timing of HSCT and conditioning regimen in AA/PNH is the same as for acquired SAA outlined above.

Constitutional SAA

There is increasing awareness that constitutional SAA, including Fanconi anaemia and dyskeratosis congenita (DC) may not only present in childhood but also in adults, often with more subtle clinical features of the syndrome.

Allo-HSCT is the only treatment able to restore normal haemopoiesis in patients with Fanconi anaemia. Patients who have a suitably matched donor and who are transfusion-dependent should be transplanted at a young age, as outcomes are best before the age of 10 years. For matched siblings, excellent survival has been obtained with low dose CY alone (60 mg/kg).[163] In a recent very large EBMT study, the optimal conditioning regimen was an irradiation-free, fludarabine-based conditioning regimen.[164] Standard doses of chemotherapy and/or irradiation should be absolutely avoided in Fanconi anaemia HSCT, because of the underlying defect in DNA repair. BM stem cells should be used in preference to PBSC, as the latter is an independent risk factor for later second malignancy. In the absence of a matched sibling donor, a suitably matched UD should be considered, also using a fludarabine-based regimen, but the addition of low-dose irradiation may be indicated (and also for those patients with clonal evolution) because of a higher risk of graft rejection.

For DC, most of published data concerning HSCT relate to X-linked DC and indicate high mortality from liver and respiratory failure, as a consequence of the more recently recognized clinical features of DC, namely pulmonary fibrosis and cirrhosis. There are only anecdotal reports of HSCT for autosomal dominant DC because of TERC or TERT mutations in association with SAA. The state of organ damage (lung, gastrointestinal, liver) is an important factor for the eligibility of the patient for HSCT. For all types of SAA associated with DC, a RIC regimen incorporating fludarabine is currently recommended.[165,166] Discussion with a specialist in BMF is advised regarding possible HSCT.

Solid tumours

Auto-HSCT. Supported by a strong rationale from laboratory studies and apparently 'convincing' results of early phase II studies, in the nineties, high-dose chemotherapy with auto-HSCT was uncritically adopted as a potentially curative option for solid tumours. For this reason, randomized trials comparing high-dose therapy with conventional control arm were difficult to conduct.

As a result, the number and size of clinical studies initiated (and often abandoned before completion) to prove or disprove its value was largely insufficient. In fact, after a quarter of century of clinical research and thousands of patients receiving high-dose therapy, the benefit of a greater escalation of dose of chemotherapy with auto-HSCT in solid tumours, with the possible exception of selected patients with breast cancer (BC) and germ cell tumours, is still unsettled.

Breast cancer (BC)

The role of auto-HSCT for primary BC at high risk of recurrence (at least four involved axillary lymph nodes) has been assessed by several randomized trials,[167] recently evaluated by a meta-analysis of individual patient data.[168] Overall, it was shown that high-dose therapy prolonged disease-free survival when used as adjuvant therapy, and showed a benefit on BC-specific survival and OS in selected cohorts of patients.[169,170] Whether auto-HSCT has benefit in the context of contemporary taxane-based regimens and targeted therapies is largely unknown. Seven phase III studies have been published in peer-reviewed journals.[167,171] Most of these trials showed improved PFS in the high-dose therapy arm, but only one an OS advantage. Six randomized trials, including 866 metastatic BC patients, have been analysed in the parallel meta-analysis of individual patient data,[168] showing a significant improvement in PFS but no improvement in OS.

Overall, based on the randomized studies so far, meta-analyses and retrospective studies,[172] auto-HSCT may still represent a therapeutic option for well-informed younger patients harbouring HER2-negative tumours and having gross involvement of axillary nodes (adjuvant setting) or highly chemosensitive disease (advanced setting).

Germ cell tumours

High-dose therapy is not recommended as first-line therapy in this setting.[173] In relapsed germ cell tumour, high-dose therapy is considered to be a therapeutic option,[174,175] especially when poor prognostic factors are present.[176] A randomized study comparing conventional dose therapy with high-dose therapy is planned. Auto-HSCT is a standard of care for patients who are (primary) refractory to platinum-based chemotherapy or for those with a second or further relapse, excluding primary mediastinal disease.[173] Multiple intensified cycles with carboplatin/etoposide is recommended as the standard high-dose treatment for germ cell tumour also owing to concerns that using a three-drug regimen would require dose reductions of the two most active drugs in this disease.

Other solid tumours

Data from randomized phase III studies comparing high-dose vs conventional-dose chemotherapy for first-line treatment of advanced ovarian cancer and limited or extensive small cell lung cancer[177,178] have shown no statistically significant difference in PFS or OS. Limitations due to study design, difficulty in recruitment and toxicity may have accounted for the lack of favourable results, that were expected based on previous phase II and retrospective analyses[179] of such highly chemosensitive diseases.

In other chemosensitive histologies, including sarcomas and central nervous system tumours, data regarding autologous transplantation in adult patients are limited, again based on clinical trials without randomization and retrospective analyses.[179] For this reason, high-dose therapy cannot be recommended as standard of care and should be considered within prospective studies when available. High-dose therapy can be regarded as a potential clinical option in selected patients with Ewing's sarcoma [180,181] and medulloblastoma.[182]

Allogeneic setting. There is no clinical experience of allografting in renal cell cancer that is TKI- and mTOR-refractory; nowadays, allo-HSCT should be considered, in renal cell cancer[183] and other solid tumours.[184,185] only in the context of prospective studies. Attempts to improve the therapeutic index of allo-HSCT in solid tumours by innovative clinical strategies are underway.[186]

Cell therapy. Despite the great potential, cell therapy programs for cancer control still have a marginal role in the management of patients with solid tumours, although its use in the setting of melanoma and other malignancies[187–189] seems ready for development as a routine therapy. This is due to limitations inherent to the technologies and products employed, and to the financial and structural burdens that are associated with cell therapy.[190] This issue should be regarded as a priority for medical oncology and cell therapy/transplantation societies.

The story of SCT in solid tumours demonstrates the importance of adopting an internationally co-ordinated approach to the investigation of this treatment modality. There needs to be an increased emphasis on prospective trials that are statistically robust and have well-defined criteria for patient selection. Only these will be able to demonstrate whether HSCT, alone or incorporated into programs with novel therapeutic modalities, is worthwhile in patients for whom conventional treatments have often limited impact on survival.

Autoimmune diseases (AD)

Auto-HSCT should be considered for patients with severe AD progressing despite standard established and/or approved therapy. It has shown long-term prolonged survival with various degrees of evidence according to each AD-specific conditions. Patients should be referred to a centre with JACIE accreditation or equivalent, where appropriate inter-disciplinary interaction with combined haematological and AD specialists allow selection and management of AD patients. Local or central biobanking, within regulatory requirements, is essential to provide adequate serum, plasma and cell samples in addition to biological samples according to each AD category and organ involvement at baseline, during the immunosuppression-free remission, and at potential relapse.

Adult patients with the underlying AD should be considered as indications for auto-HSCT, when presenting: a) severe systemic sclerosis and disease duration (i) of less than 5 years since onset of first non-Raynaud's symptoms and a modified Rodnan skin score $\geqslant 15$ *plus* respiratory (with a diffusing capacity of the lung for carbon monoxide and/or forced vital capacity $\leqslant 80\%$ of predicted *and* evidence of interstitial lung disease on high resolution computed tomography scan), cardiac (with conduction or rhythm disturbance, pericarditis) or renal involvement or (ii) of less than 2 years and no major organ dysfunction as defined above provided they had a modified Rodnan skin score of at least 20 and an acute phase response (level I);[191] b) multiple sclerosis in the relapsing-remitting phase, showing high clinical and MRI inflammatory activity, with rapid deterioration despite the use of one or more lines of approved treatments; the 'malignant' (Marburg) forms and the secondary progressive disease, only when some inflammatory activity is still evident, with clinical relapses and/or new T2 MRI lesions on two subsequent scans, and with a sustained and increased in disability in the previous year and with an EDSS upper limit of 6.5, except for the malignant form (level II);[192,193] c) systemic lupus erythematosus early in the disease course, with sustained or relapsed activity defined by a BILAG A category, with either kidney (with a creatinine clearance >30 ml/min/m^2 on renal biopsy of less than 12 months showing evidence of WHO class III or IV glomerulonephritis), neurologic, cardiovascular or pulmonary, vasculitis or autoimmune cytopenias after at least 6 months of the best standard therapy, using mycofenolate mofetil or CY with or without anti-CD20 (level II);[53] d) Crohn's

disease, refractory to immunosuppressive agents and anti-TNF monoclonal antibodies, with sustained endoscopic or CT scan-proven activity or extensive disease in which surgical resection would expose the patient to the risk of small bowel syndrome or with refractory colonic disease and perianal lesions where coloprotectomy with a definitive stoma not accepted by the patient (level II); e) autoimmune cytopenias with either immune thrombocytopenia, autoimmune haemolytic anaemia and Evans' syndrome refractory to at least two lines of treatment (including rituximab and TPO-receptor agonists for immune thrombocytopenia) (level II); f) for other AD, including rheumatoid arthritis, systemic vasculitis, dermatomyositis and polymyositis can be considered as exceptional indications. Chronic demyelinating inflammatory polyneuropathy and neuromyelitis optica, type 1 diabetes mellitus, refractory type II coeliac disease, autism spectrum disorders potentially respond, but experience of auto-HSCT has been relatively recent and patients should only be treated on approved prospective clinical trials.

Syngeneic as an alternative to auto-HSCT may be considered with comparable risks and potential greater benefit according to donor-related issues. Allo-HSCT outside of a clinical trial is highly discouraged in all ADs except for patients with immune thrombocytopenia, autoimmune haemolytic anaemia and Evans' syndrome refractory to at least two lines of treatment (including rituximab and TPO-receptor agonists for immune thrombocytopenia) under the CO criterion.[52]

Both for adult and paediatric indications, specific recommendations include patient selection, stem cell collection, graft manipulation, conditioning regimens and supportive care. Comprehensive cardiopulmonary screening and pre-transplant evaluation are critically important to exclude patients at high risk of NRM.[194]

Priming chemotherapy is recommended to enhance mobilization whilst maintaining disease control and to prevent potential flare, which may be a consequence of G-CSF alone (level I). The recommended mobilization regimen is CY at 2–4 g/m^2 with uromixetan and cautious hyper hydration followed by G-CSF 5–10 mcg/kg (level II). A minimum dose of 2×10^6/kg CD34+ cells should be reinfused, irrespective of any graft manipulation (level II). Among the many conditioning regimens reported, the ADWP recommends CY 200 mg/kg with polyclonal or monoclonal anti-T-cell serotherapy generally, with CY 120 mg/kg, fludarabine 150 mg/kg and anti-T-cell serotherapy as an alternative in paediatrics and BEAM+anti-T-cell serotherapy in multiple sclerosis specifically. After HSCT, all patients should remain under the direct routine combined care of the transplant and the AD specialists for at least the first 100 days post transplant, and then on a quarterly basis for the first 2 years even if clinically stable. Thereafter, joint annual review as a minimum is recommended. Long-term annual data reporting, including late effects, of all AD patients after HSCT to registries is a minimum recommendation.[52]

STATUS OF TRANSPLANTS IN SPECIFIC DISEASES IN CHILDREN AND ADOLESCENTS

More than 20% of allo-HSCT are performed in patients below 20 years. However, at least one-third of HSCTs in children are performed for rare indications. Clinical trials to improve outcomes after HSCT in children have been limited by small numbers and disease-specific complications. Distinct side and late effects are exclusively related to the vulnerability of the developing organism, including child-specific organ dysfunction, delayed hormonal development, growth retardation, dental and skeletal damage, and the high risk of malignancies in congenital disorders with chromosomal breakage syndromes. During the last years, better HLA matching with non-sibling donors, the evolution of RIC regimen, better supportive care and better diagnosis of infectious complications, dramatically reduced NRM. That enabled offering allo-HSCT at an earlier disease course with better performance status and not as 'last chance for cure'. However, the burden of acute and especially chronic GVHD is still a major limitation for patients who do not identify well-matched donors and have to be considered for outweighing the risk of this procedure. In such situations, nowadays HSCT from haploidentical family donors or from an unrelated CB might be performed within clinical studies in highly experienced and specialized centres.

Acute myeloid leukaemia (AML)

Childhood AML is a rare and heterogeneous disease, cure rates with intensive chemotherapy and extensive supportive care are around 60%. Better outcomes are reported for patients with favourable prognostic markers.[195] Hence, HSCT is not recommended as a front-line therapy for good-risk patients with AML.[196,197] Allo-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 EFS ranging from 55 to 72%.[198,199] Infant AML and children with FAB M0, M6 or M7 AML, who stand very poor chances of cure by chemotherapy or by auto-HSCT, are indications for HSCT in first remission.[200] 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.[201,202]

Auto-HSCT has been used as consolidation in children with AML, in CR1 after induction therapy and represented a possible alternative for high-risk children lacking a matched donor. Nevertheless, results of paediatric studies comparing auto-HSCT to chemotherapy were conflicting and are currently not recommended outside prospective trials addressing new questions.[203] Children who experience AML relapse and who reach second remission are candidates for any kind of allo-HSCT. To improve remission quality, and to reduce post-transplant relapse, several studies are on the way, exploring new immunological mechanisms and pharmaceutical developments.

Acute lymphoid leukaemia (ALL)

The indications for HSCT in children with ALL in CR1 are limited to the subpopulation of high-risk ALL. Most study groups define these patients as having estimated EFS of less than 50%. The risk factors indicating the usefulness of HSCT are known molecular biological markers or chromosomal abnormalities, and biological factors including poor prednisone response, and resistance to initial chemotherapy including persistence of MRD.[204] MRD became the most important prognostic factor for ALL relapse in children and should be used for better discrimination of high-risk and very high-risk groups.[205,206] For the latter patients, allo-HSCT from matched sibling donors or a well-matched unrelated donor and for the highest risk category also a mismatched donor is an option. Also, infants with very high-risk features benefit from allo-HSCT and are candidates for both related and well-matched unrelated HSCT.[207] ALL patients, who experience an early or very early marrow relapse, still have a dismal prognosis when treated with conventional chemotherapy.[208] Although nearly 90% achieve a second remission, most of them subsequently develop progressive disease. Both matched sibling donor HSCT and well-matched unrelated donor HSCT are clearly indicated in these patients since the outcomes are similar.[209,210] 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 can be indicated.[19,211] In contrast to adults, PBSC from HLA-compatible sibling donors show no advantage for engraftment, relapse incidence and OS compared with BM and therefore BM is the preferred stem cell source for children.[212]

Non-Hodgkin lymphoma

Nearly all children and adolescents are cured with multidrug chemotherapy. Only few patients are eligible for allo-HSCT: patients with residual disease after re-induction therapy of contemporary chemotherapy-protocols or patients with early NHL relapses and patients with inadequate response or relapse of anaplastic lymphoma kinase-positive anaplastic large cell lymphoma.[213–215] All other approaches should be discussed with the experts of the front line chemotherapy trials.

Chronic myeloid leukaemia (CML)

Although allo-HSCT is the only curative option for patients with CML, the introduction of specific TKI has substantially modified the treatment strategies for all age groups. As children and adolescents have to be treated for an indefinite time with TKI, it has become clear that toxicities may make long-term TKI therapy less attractive compared with allo-HSCT.[216,217] HSCT has long-term complications of growth failure, infertility, chronic GVHD, metabolic syndrome and secondary malignancies, whereas prolonged TKI may cause growth failure, hepatic and cardiac complications.[216–218] Nowadays, it is accepted that all children and adolescents with CML-CP should initially be treated with imatinib and maintained with TKI therapy indefinitely if there is a good response.[219,220] No long-term results are evaluable to show whether children will stay in sustained complete molecular remission after TKI discontinuation. Further, it is considered that allo-HSCT with an HLA-identical sibling donor or closely matched unrelated donor is a clinical option for patients with treatment failure or recurrence after receiving salvage second-generation TKI treatment.[221] Further, it is considered that allo-HSCT with an HLA-identical sibling donor or closely matched unrelated donor can be considered for patients with treatment failure or recurrence after receiving salvage second-generation TKI treatment. However, prospective cooperative studies are needed to address this complex issue in young patients with CML.[220,222]

MDS, juvenile myelomonocytic leukaemia

Allo-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, as well as secondary AML.[223–225] The role of auto-HSCT in children with MDS remains controversial and is generally not recommended.

Inherited diseases

Primary immunodeficiencies. Primary immunodeficiencies are genetic disorders characterized by defective or impaired innate or adaptive immunity. Of these, severe combined immunodeficiencies are the most severe, leading to death in infancy or early childhood unless treated appropriately. Many other immunodeficiencies lead to decreased quality of life with premature death through childhood or early adulthood. Recurrent, persistent or opportunistic infections are the classic hallmarks of primary immunodeficiencies, although immunodysregulation or malignancies are increasingly recognized presentations. Allo-HSCT can cure most cellular immunodeficiencies affecting innate or adaptive immunity. Advances in a number of areas including earlier diagnosis, more accurate HLA-typing, an increasing range of stem cell sources, less toxic conditioning regimens and improved supportive care have enabled increasing successful outcomes, of over 90% survival in some conditions. 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 actively participating within EBMT's inborn errors working party. The guidelines for each particular inherited condition are published on the EBMT's website and reviewed regularly by the Inborn Errors working party members.[226] Allo-HSCT is indicated for severe primary immunodeficiencies from both HLA-identical and alternative donors, including umbilical CB.

Severe combined immunodeficiency. The diagnosis of SCID is a paediatric emergency, and these patients should undergo HSCT as soon as possible. An allo-HSCT results in a survival rate of more than 90% when carried out shortly after birth.[227] Factors that influence prognosis include the age, the type of SCID (B lymphocyte+ vs B lymphocyte −), and the clinical state at the time of diagnosis, in particular the presence of viral respiratory 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 (particularly those with an absence of NK cells) 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 T lymphocyte function after transplant. The restoration of B lymphocyte function nearly always occurs in patients with the B lymphocyte +ve form of SCID, but is absent in 40% of those with a B lymphocyte − ve form. In the absence of an HLA-identical family donor, HSCT from a partially HLA-compatible donor is recommended. In this respect, the use of a conditioning regimen has a positive effect on survival in the B lymphocyte—SCID group but not in 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, with improving outcomes.[228]

Other primary immunodeficiencies. Allo-HSCT can cure most of the T lymphocyte immunodeficiencies, Wiskott-Aldrich syndrome, phagocyte disorders such as leukocyte adhesion deficiency and chronic granulomatous diseases, haemophagocytic syndromes such as familial lymphohistiocytosis, and a growing number of other immunodeficiencies. These patients require conditioning. As for patients with SCID, prognostic factors include age at transplant, the type of primary immunodeficiency, and the clinical state at the time of diagnosis, in particular, the presence of viral respiratory infection, and the degree of HLA histocompatibility. Survival is similar using an HLA-identical family donor or HLA-matched unrelated donor.[228] Patients transplanted at an early age have a better outcome than those transplanted when older.

Inherited diseases: metabolic diseases. Most of the metabolic diseases considered for HSCT are lysosomal storage diseases that rely on transfer of enzyme from donor-derived blood cells to the reticuloendothelial system and solid organs. The successful outcome of HSCT can be affected by the lack of engraftment (secondary rejection is comparatively common), the enzyme levels of the donor (lower if they are a sibling carrier of the disease), and the degree of sustained donor chimerism and possibly by the immune processes directed against the normal donor enzyme. CB transplantation is particularly successful in patients with Hurler's Syndrome.[229] In diseases with the central nervous system involvement, amelioration is dependent on the replacement of recipient 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 predict the quality of life 18 months beyond the first consideration of HSCT

(allowing for a donor search, clinical assessment and conditioning).

Aplastic anaemia, pure red cell aplasia (Blackfan-Diamond) and Fanconi anaemia

An allo-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 one option for patients who lack an HLA-compatible family donor. The search for an unrelated donor should be initiated before they receive the immunosuppressive therapy. An alternative option for children who lack an HLA-compatible family donor is upfront matched unrelated donor HSCT if a donor is readily available, as results of MUD HSCT in children are now similar to matched sibling HSCT.[230–234] 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 clinical status. Children with Blackfan-Diamond anaemia having a matched sibling should be transplanted if they do not respond to steroids.[235] Children with FA should be transplanted if they have a 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

The outcome of HSCT for thalassaemia has progressively improved with the identification of the Pesaro Classes of Risk and the development of new conditioning regimens and supportive therapies. Allo-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.[29] Extended haplotype matching seems to impact positively on prognosis after unrelated donor HSCT.[236–240] Developments of conventional therapy have improved both the quality and the duration of life for patients with sickle cell disease; however, today a prediction on the severity and onset of complications is not possible. For this reason, HSCT from an HLA-identical sibling or—for a small subset of patients—from a well-matched non-sibling donor should be offered.[241–244]

Solid tumours

Neuroblastoma (stage 4 beyond the age of 1 year, or high-risk factors in lower stages) is still the only indication where the benefit of auto-HSCT has been demonstrated by randomized trials.[245,246] Although to date the published results do not demonstrate an unequivocal benefit for consolidation with HDT, children and adolescents with solid tumours might undergo auto-HSCT following 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 and Wilm's tumour: relapse.

Generally, allo-HSCT in children with solid tumours should only be explored within prospective trials in highly experienced centres.

Autoimmune diseases

For paediatric patients, auto-HSCT is a CO for carefully selected subpopulations of patients with juvenile inflammatory arthritis with polyarticular course or polyarticular onset, no response to equivalent prednisone dose of 2 mg/kg/day (max 60 mg daily) for eight consecutive weeks, and inadequate response to, or intolerance to, at least two disease modifying antirheumatic drugs, including biological agents or unacceptable toxicity from disease modifying antirheumatic drugs or corticosteroid therapy (level II), for SSc, systemic lupus erythematosus, Crohn's disease which requires special consideration and appropriate expertise in patient selection (level III), autoimmune cytopenia where no fully HLA compatible sibling or unrelated donor can be identified, or in patients with Evans' syndrome with no 9/10 HLA matched unrelated donor (level II).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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