



This is a repository copy of *Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022.*

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/187847/>

Version: Published Version

---

**Article:**

Snowden, J.A. [orcid.org/0000-0001-6819-3476](https://orcid.org/0000-0001-6819-3476), Sánchez-Ortega, I., Corbacioglu, S. et al. (17 more authors) (2022) Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. *Bone Marrow Transplantation*, 57 (8). pp. 1217-1239. ISSN 0268-3369

<https://doi.org/10.1038/s41409-022-01691-w>

---

**Reuse**

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:

<https://creativecommons.org/licenses/>

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.



[eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk)  
<https://eprints.whiterose.ac.uk/>

## FEATURE OPEN



# Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022

John A. Snowden<sup>1</sup>✉, Isabel Sánchez-Ortega<sup>2</sup>, Selim Corbacioglu<sup>3</sup>, Grzegorz W. Basak<sup>4</sup>, Christian Chabannon<sup>5</sup>, Rafael de la Camara<sup>6</sup>, Harry Dolstra<sup>7</sup>, Rafael F. Duarte<sup>8</sup>, Bertram Glass<sup>9</sup>, Raffaella Greco<sup>10</sup>, Arjan C. Lankester<sup>11</sup>, Mohamad Mohty<sup>12</sup>, Bénédicte Neven<sup>13</sup>, Régis Peffault de Latour<sup>14</sup>, Paolo Pedrazzoli<sup>15</sup>, Zinaida Peric<sup>16</sup>, Ibrahim Yakoub-Agha<sup>17</sup>, Anna Sureda<sup>18</sup>, Nicolaus Kröger<sup>19</sup> for the European Society for Blood and Marrow Transplantation (EBMT)

© The Author(s) 2022

For over two decades, the EBMT has updated recommendations on indications for haematopoietic cell transplantation (HCT) practice based on clinical and scientific developments in the field. This is the eighth special EBMT report on the indications for HCT for haematological diseases, solid tumours and immune disorders. Our aim is to provide general guidance on HCT indications according to prevailing clinical practice in EBMT countries and centres. In order to inform patient decisions, these recommendations must be considered in conjunction with the risk of the disease, risk of HCT procedure and non-transplant strategies, including evolving cellular therapies. HCT techniques are constantly evolving and we make no specific recommendations, but encourage harmonisation of practice, where possible, to ensure experience across indications can be meaningfully aggregated via registry outputs. We also recommend working according to JACIE accreditation standards to maintain quality in clinical and laboratory components of practice, including benchmarking of survival outcomes. Since the last edition, the COVID-19 pandemic has affected clinical decision making and activity across indications. Although the full impact of the pandemic is yet to be determined, we recommend that decision making across indications is delivered with ongoing reference to EBMT and national COVID-19 guidance, in accordance with current local conditions.

*Bone Marrow Transplantation*; <https://doi.org/10.1038/s41409-022-01691-w>

## INTRODUCTION

This is the eighth report from the European Society for Blood and Marrow Transplantation (EBMT) covering indications for haematopoietic cell transplantation (HCT) according to prevailing clinical practice in EBMT countries and centres [1]. For over two decades, EBMT has considered changes in HCT practice alongside developments in non-transplant treatments. As in previous editions, these 2022 recommendations are based upon clinical trials, registry data, and the opinion of EBMT experts from the board, scientific council and relevant working parties, but not upon a formal extensive or systematic review of the literature. They aim to provide general guidance on transplant indications to inform individual patient decisions by the multidisciplinary team (MDT). They must be considered in conjunction with the risk of the

disease status, the likelihood of the successful outcome of HCT, assessment of patient co-morbidities and estimation of treatment-related mortality (TRM) risk alongside the results of non-transplant strategies. Besides potential survival benefits, assessment must include quality of life and late effects. The recommendations are not intended to be used to choose a particular transplant protocol, conditioning regimen or stem cell source, but we encourage harmonisation of practice, where possible, to ensure meaningfully aggregated experience across indications via registry outputs.

Since the last update, we have experienced the Coronavirus disease-19 (COVID-19) pandemic, which has affected HCT activity for a variety of reasons, from risks to patients, availability of donors and stem cell products, through to maintenance of staffing and services [2]. Waves of the pandemic impacted variably across our

<sup>1</sup>Department of Haematology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK. <sup>2</sup>EBMT Executive Office, Barcelona, Spain. <sup>3</sup>University of Regensburg, Regensburg, Germany. <sup>4</sup>Department of Hematology, Transplantation and Internal Medicine, University Clinical Centre, Medical University of Warsaw, Warsaw, Poland. <sup>5</sup>Institut Paoli Calmettes Comprehensive Cancer Center & Centre d'Investigations Cliniques en Biothérapies Inserm CBT-1409, Marseille, France. <sup>6</sup>Hematology, Hospital de la Princesa, Madrid, Spain. <sup>7</sup>Laboratory of Hematology, Department of Laboratory Medicine, Radboud University Medical Center, Nijmegen, The Netherlands. <sup>8</sup>Hospital Universitario Puerta de Hierro Majadahonda—Universidad Autónoma de Madrid, Madrid, Spain. <sup>9</sup>Klinik für Hämatologie und Stammzelltransplantation, HELIOS Klinikum Berlin-Buch, Berlin, Germany. <sup>10</sup>Haematology and Bone Marrow Transplant Unit, IRCCS San Raffaele Scientific Institute, Milano, Italy. <sup>11</sup>Willem-Alexander Children's Hospital, Leiden University Medical Center, Leiden, The Netherlands. <sup>12</sup>Sorbonne University, Saint-Antoine Hospital (AP-HP), INSERM UMRs 938, Paris, France. <sup>13</sup>Pediatric Immuno-hematology Unit, Necker Children Hospital, Assistance Publique Hôpitaux de Paris, Université de Paris Cité, Paris, France. <sup>14</sup>Saint-Louis Hospital, Paris Diderot University, Paris, France. <sup>15</sup>Fondazione IRCCS Policlinico San Matteo and University of Pavia, Pavia, Italy. <sup>16</sup>Department of Hematology, University Hospital Centre Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia. <sup>17</sup>CHU de Lille, Univ Lille, INSERM U1286, Infinite, 59000 Lille, France. <sup>18</sup>Institut Català d'Oncologia—Hospital Duran i Reynals, Barcelona, Spain. <sup>19</sup>University Medical Center Hamburg, Hamburg, Germany. ✉email: john.snowden1@nhs.net

Received: 22 March 2022 Revised: 15 April 2022 Accepted: 20 April 2022

Published online: 19 May 2022

geographical regions, requiring broader public health measures, including the uptake of vaccination. From an early stage, there was recognition that outcomes following HCT and CAR-T cell therapies were poorer in patients in whom SARS-2-CoV infection was detected and also a response to vaccination is reduced and variable in the HCT setting. The EBMT regularly updates recommendations for SARS-CoV-2 management and vaccination (<https://www.ebmt.org/covid-19-and-bmt>). Consequently, there has been a temporary reduction in HCT rates in some indications, with necessary prioritisation between indications and delays in treatment that may have impacted upon outcomes of HCT. Although the full impact of the pandemic is yet to be determined and our understanding and evidence-base is evolving, we recommend that decision making across indications is made by an MDT with reference to EBMT and other national guidance in relation to COVID-19, and in accordance with current local conditions.

This guidance does not primarily intend to cover cellular therapies, but makes reference to the application of CAR-T cells as a treatment option alongside HCT in acute lymphoblastic leukaemia (ALL) and lymphomas, and, more developmentally, in multiple myeloma, chronic lymphocytic leukaemia and acute myeloid leukaemia.

Importantly, we recognise that there is an overlap between adult and paediatric indications, particularly in the 'teenager and young adult' (TYA) group, and definitions of paediatric and TYA (and therefore 'adult' care) vary internationally. Despite the age cut-offs, which are also influenced by EBMT registry definitions, the indications should be interpreted with flexibility, particularly in the TYA age group and some 'paediatric' and TYA indications may occasionally extend into older adult age groups. Given this consideration, we have combined 'Inherited diseases' into considerations for all ages, although the predominant use of HCT will be for the paediatric age group.

## TRANSPLANT CATEGORISATION, DEFINITIONS AND FACTORS

### Haematopoietic cell transplant

HCT refers to any procedure where haematopoietic stem cells (HSC) of any donor type and source are given to a recipient with the intention of repopulating and replacing the haematopoietic system in total or in part. HSC for HCT can be derived from bone marrow (BM), peripheral blood (PB) or cord blood (CB).

### Donor categories and stem cell sources

Donor type is categorised as autologous, syngeneic and allogeneic, the latter being either related or unrelated. Beyond HLA-matched related (i.e., sibling) donors (MSD), a well-matched unrelated donor (MUD) is defined as a 10/10 identical unrelated donor (UD) based on HLA high-resolution typing for class I (HLA-A, -B, -C) and II (HLA-DRB1, -DQB1). A mismatched unrelated donor (MMUD) refers to a UD mismatched in at least one antigen or allele at HLA-A, -B, -C, -DR or -DQ and a haploidentical donor refers to one haplotype mismatched donor, most frequently being a family donor. Criteria for UD selection have been proposed [3, 4], but are beyond the scope of these recommendations and incorporation into clinical practice will depend on the effort from donor registries and transplant centres balanced against strategies to incorporate mismatched alternative donors (MMAD), including haploidentical donors, into practice.

Recent developments include non-T-cell-depleted haploidentical HCT, mainly with post-transplant cyclophosphamide (PTCy) as graft-versus-host disease (GVHD) prophylaxis that has led to a reduction in chronic GVHD and TRM [5] in this setting. In parallel, results of unrelated and mismatched unrelated transplants are continually improving, and studies (mostly registry based) have shown similar outcomes of 10/10 HLA compatible unrelated transplants compared with HCT from an MSD [2]. Moreover,

several retrospective studies have shown similar results for haploidentical HCT with PTCy to MSD and MUD [6–10]. However, additional studies are needed to confirm these findings for particular indications. Therefore, in this current version, we continue to combine the recommendations for MMAD, incorporating CB, haploidentical and MMUD into a single category separate from well-matched related and UD. Beyond this general approach, the relative value of the various modalities is described and addressed in more detail below in sections for the relevant indications.

Transplant decisions derive not only from sound clinical and scientific evidence but also from each centre's research priorities, local expertise, cost considerations and ease of access to particular transplant modalities, along with individual patient and donor preference. Ultimately, we recommend all aspects are brought together and documented in an MDT meeting.

## CATEGORISATION OF TYPE OF INDICATION FOR TRANSPLANT PROCEDURES

EBMT indications are classified into four categories (Table 1), to describe the levels of evidence and recommendations for types of transplants and different indications.

### Transplant indications in adults

The updated 2022 classification of HCT procedures in adults is shown in Table 2.

*Acute myeloid leukaemia (AML).* As per EBMT's last activity survey, AML accounts for more than one-third of allo-HCT transplants [2]. The heterogeneity of AML, response to treatment and associated morbidity and TRM of HCT mandates risk stratification based on patient, disease, and transplant parameters [11, 12], which has led to significant improvement in outcomes for AML in recent years [13]. Genetic risk factors form the basis of modern prognostication for predicting outcome in AML patients and guide decisions in relation to HCT as a post-remission treatment modality [14–16], including cytogenetics [14, 15, 17], molecular mutations [16, 18, 19] and post-induction measurable residual disease (MRD) status [20–22]. Alongside hematopoietic cell transplantation-specific comorbidity index (HCT-CI) [23], data-mining-based machine-learning algorithms may improve prediction of day +100 mortality post-HCT [24]. Transplant techniques, including improvements in supportive care, prevention and treatment of infective complications and reduced intensity conditioning, have led over the last 20 years to almost a 50% reduction in TRM [14] and increasing treatment of patients over the age of 65 years [25].

Overall, allo-HCT in first complete remission (CR1) is recommended for adverse and intermediate-risk AML as defined by the European LeukemiaNet (ELN) risk stratification that is based on cytogenetics and mutational phenotype, while HCT is not recommended for AML patients with favourable disease [1, 14]. Specifically, HCT in CR1 is recommended for AML patients with adverse cytogenetics [1, 14] and patients with normal cytogenetics with unmutated NPM1 plus high FLT3-ITD allele ratio or those harbouring RUNX1, ASXL1, or TP53 mutations. However, HCT is not recommended in CR1 in the favourable risk group, including AML patients with core-binding factor (CBF) that are associated with translocations t(8;21), inv(16) or t(16;16) and NPM1 mutation plus wild-type FLT3-ITD or FLT3 with low-allele ratio (<0.5) (although this may be controversial) [1, 14].

Allo-HCT may be effective in a subset of patients with primary refractory AML (defined as failure to achieve CR after two cycles of induction chemotherapy) and relapsing AML [26], especially those achieving CR2 [27]. However, patients with resistant disease should be considered for novel transplant approaches, including trials of CAR-T cells [19]. All types of donors should be considered for suitably fit, adverse risk patients with AML, while those with

**Table 1.** EBMT categorisation of type of indication for transplant procedures and strength of evidence.

Categories	Settings where HCT ought to be performed
Standard of care (S)	Indications 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 HCT 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 in HCT and an appropriate infrastructure as defined by the JACIE standards.
Clinical option (CO)	Indications for which the results of small patient cohorts show efficacy and acceptable toxicity of the HCT procedure, but confirmatory randomised studies are missing, often as a result of low patient numbers. 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 that HCT is a valuable option for individual patients after careful discussions of risks and benefits with the patient, but that for groups of patients the value of HCT needs further evaluation. Transplants for indications under this heading should be performed in a specialist centre with major experience in HCT with an appropriate infrastructure as defined by JACIE standards.
Developmental (D)	Indications when the experience is limited, and additional research is needed to define the role of HCT. These transplants should be done within the framework of a clinical protocol, normally undertaken by transplant units with acknowledged expertise in the management of that particular disease or that type of HCT. Protocols for D 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. Centres performing transplants under this category should meet JACIE standards.
Generally not recommended (GNR)	Comprises a variety of clinical scenarios in which the use of HCT cannot be recommended to provide a clinical benefit to the patient, including early disease stages when results of conventional treatment do not normally justify the additional risk of an HCT, very advanced forms of a disease in which the chance of success is so small that does not justify the risks for patient and donor, and indications in which the transplant modality may not be adequate for the characteristics of the disease. A categorisation as GNR does not exclude that centres with particular expertise on a certain disease can investigate HCT in these situations. Therefore, there is some overlap between GNR and D categories, and further research might be warranted within prospective clinical studies for some of these indications.
Grade	<i>Strength of the evidence supporting the assignment of a particular category</i>
Grade I	Evidence from at least one well-executed randomised trial.
Grade II	Evidence from at least one well-designed clinical trial without randomisation; cohort or case-controlled analytic studies (preferably from more than one centre); multiple time-series studies; or dramatic results from uncontrolled experiments.
Grade III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports from expert committees.

intermediate risk are usually transplanted using MSD or 10/10 UD [1].

AML patients in the favourable risk category may be considered for auto-HCT especially if they are MRD negative post induction therapy [1, 14], while patients with persistent MRD should be considered for allo-HCT [28]. Low levels of CBF fusion gene transcripts may persist after the end of treatment without affecting survival. However, failure to achieve a 3-log reduction in CBF fusion transcript after two cycles of chemotherapy is associated with a high risk of relapse and these patients might benefit from allo-HCT [29, 30]. Younger adults with NPM1-mutated AML and MRD positivity by RQ-PCR in the PB after two cycles of chemotherapy have higher rates of relapse and should be considered for allo-HCT [31]. Standard-risk younger patients with NPM1-unmutated AML with positive MRD by multi-parametric flow cytometry seem to benefit from HCT in CR1 [32]. Although controversial, auto-HCT [1] may also be considered for intermediate-risk patients and offered for AML-M3 patients achieving CR2 and MRD negativity [1].

**Acute lymphoblastic leukaemia (ALL).** As per EBMT's latest activity survey, ALL is the second most common indication for allo-HCT, accounting for 17% of cases [2], with Ph-negative ALL in CR as the major proportion [33]. Having been originally established on donor versus no donor studies and subsequent meta-analyses, allo-HCT continues to be the standard of care in high-risk ALL patients defined by conventional risk factors and MRD status (i.e., adverse cytogenetics, slow remitters, after failure or inability to

receive a paediatric-inspired regimen) and in relapsed ALL, but is not indicated for standard-risk ALL, especially if MRD negative [34–38].

Results of allo-HCT from UD are constantly improving as those from non-T-cell-depleted haploidentical donors, as alternatives for transplant-eligible ALL patients lacking a MSD [39, 40]. Importantly, in recent years, the treatment paradigm for primary refractory and relapsed Philadelphia (Ph) negative ALL has been revolutionised with the introduction of blinatumomab, a first-in-class bispecific T-cell engager anti-CD19 monoclonal antibody (mAb) and the drug conjugate, inotuzumab ozogamicin, an anti-CD22-calicheamicin mAb. In addition, anti-CD19 CAR-T cell therapy was recently approved for patients up to 25 years old [41–43]. This therapeutic progress is additional to Ph-positive ALL by tyrosine kinase inhibitors (TKIs) [44]. Furthermore, MRD monitored throughout the therapy pathway, guides treatment and is important for decision making [45]. Whether standard-risk ALL patients achieving MRD negativity in CR1 on paediatric-inspired treatment protocols should undergo HCT is a matter of debate, while those with persistent MRD post-consolidation should proceed to allo-HCT [46–49].

High-risk cytogenetics at diagnosis is an indication for allo-HCT, even in MRD-negative patients, at least until additional studies are available [50–52]. Adverse cytogenetics include, but are not limited to, low hypodiploidy, KMT2A (previously MLL) translocations, t(8;14), complex karyotype ( $\geq 5$  chromosomal abnormalities) and Ph-positive ALL.

**Table 2.** Proposed classification of transplant indications for adults—2022.

Disease	Disease status	MSD allo	MUD allo	MMAD allo	Auto	CAR-T
<i>Haematological malignancies</i>						
AML <sup>a</sup>	CR1 (favourable risk and MRD <sup>-</sup> ) <sup>b</sup>	GNR/II	GNR/II	GNR/II	CO/I	
	CR1 (favourable risk and MRD <sup>+</sup> ) <sup>b</sup>	S/II	CO/II	CO/II	GNR/II	
	CR1 (intermediate risk) <sup>b</sup>	S/II	CO/II	CO/II	CO/I	
	CR1 (adverse risk) <sup>b</sup>	S/II	S/II	S/II	GNR/I	
	CR2	S/II	S/II	S/II	CO/II	
	APL Molecular CR2	S/II	CO/II	GNR/III	S/II	
	Relapse or refractory	CO/II	CO/II	CO/II	GNR/III	
ALL <sup>a</sup>	Ph (-), CR1 (standard risk and MRD <sup>-</sup> ) <sup>b</sup>	GNR/II	GNR/II	GNR/III	CO/III	
	Ph (-), CR1 (standard risk and MRD <sup>+</sup> ) <sup>b</sup>	S/II	CO/II	CO/II	GNR/II	CO/II
	Ph (-), CR1 (high risk) <sup>b</sup>	S/II	S/II	CO/II	GNR/III	
	Ph (+), CR1 (MRD <sup>-</sup> )	S/II	S/II	CO/II	CO/III	
	Ph (+), CR1 (MRD <sup>+</sup> )	S/II	S/II	S/II	GNR/II	
	CR2	S/II	S/II	S/II	GNR/II	
	Relapse or refractory	CO/II	CO/II	CO/II	GNR/III	
CML	1st CP, failing 2nd or 3rd line TKI	S/II	S/II	CO/III	GNR/II	
	Accelerated phase, blast crisis or >1st CP	S/II	S/II	CO/II	GNR/III	
Myelofibrosis	Primary or secondary with an intermediate-2 or high DIPSS score	S/II	S/II	S/III	GNR/III	
MDS	Very low and low-risk (IPSS-R)	CO/II	CO/II	CO/II	GNR/III	
	Intermediate-risk without additional factors <sup>c</sup> (IPSS-R)	CO/II	CO/II	CO/II	CO/II	
	Intermediate-risk with additional factors <sup>c</sup> (IPSS-R)	S/II	S/II	S/II	GNR/III	
	High-, very high-risk (IPSS-R)	S/II	S/II	S/II		
	sAML in CR1 or CR2	S/II	S/II			
CMML	CMML-2 or MP-CMML	S/II	S/II	S/II	GNR/III	
	CMML-0 or CMML-1 with additional risk factors <sup>d</sup>	S/II	S/II	S/II	GNR/III	
CLL	Poor risk disease refractory or relapsing after at one line of prior therapy (Richter's transformation excluded)	CO/II	CO/II	GNR/III	GNR/III	CO/II
	Richter transformation	S/II	S/II	S/II	GNR/III	CO/II
LBCL	CR1 (intermediate/high IPI at diagnosis)	GNR/III	GNR/III	GNR/III	CO/I	GNR/III
	Untested relapse	GNR	GNR	GNR	GNR	S/I
	Chemosensitive early relapse, ≥CR2	CO/II	CO/II	D/III	CO/I	S/II
	Chemosensitive late relapse, ≥CR2	CO/II	CO/II	D/III	S/II	CO/II
	Chemosensitive relapse after auto-HSCT failure	CO/II	CO/II	CO/III	GNR/III	S/II
	Refractory disease	CO/II	CO/II	CO/III	GNR/I	S/I
Primary CNS lymphoma	GNR/III	GNR/III	GNR/III	S/II	D/III	
FL	CR1, untransformed	GNR/III	GNR/III	GNR/III	GNR/II	GNR/III
	CR1, transformed into high-grade lymphoma	GNR/III	GNR/III	GNR/III	CO/III	GNR/II
	Chemosensitive relapse, ≥CR2	CO/III	CO/III	GNR/III	S/II	GNR/III
	≥CR2 after auto-HSCT failure	S/II	S/II	D/III	GNR/III	CO/II
	Refractory	CO/II	CO/II	CO/III	GNR/III	CO/II
MCL	CR1	GNR/III	GNR/III	GNR/III	S/I	GNR/III
	CR/PR >1, no prior auto-HCT	CO/III	CO/III	D/III	CO/II	S/II
	CR/PR >1, after prior auto-HCT	CO/II	CO/II	CO/III	GNR/II	S/II
	Refractory	CO/II	CO/II	CO/III	GNR/II	S/II
WM	CR1	GNR/III	GNR/III	GNR/III	GNR/III	GNR/III
	Chemosensitive relapse, ≥CR2	GNR/III	GNR/III	GNR/III	CO/II	GNR/III

Table 2. continued

Disease	Disease status	MSD allo	MUD allo	MMAD allo	Auto	CAR-T
PTCL	Poor risk disease	CO/II	CO/II	D/III	GNR/III	GNR/III
	CR1	CO/II	CO/II	GNR/III	CO/II	GNR/III
	Chemosensitive relapse, ≥CR2	S/II	S/II	CO/III	CO/II	GNR/III
	Refractory	CO/II	CO/II	CO/III	GNR/II	GNR/III
Primary CTCL	EORTC/ISCL Stages I–IIA (early)	GNR/III	GNR/III	GNR/III	GNR/III	GNR/III
	EORTC/ISCL Stages IIB–IV (advanced)	CO/III	CO/III	D/III	GNR/III	GNR/III
HL	CR1	GNR/III	GNR/III	GNR/III	GNR/I	GNR/III
	Chemosensitive relapse, no prior auto-HCT	D/III	D/III	GNR/III	S/I	GNR/III
	Chemosensitive relapse, after prior auto-HCT	S/II	S/II	S/II	CO/III	GNR/III
	Refractory	D/II	D/II	D/III	CO/III	GNR/III
MM	Upfront standard risk	CO/II	CO/II	GNR/III	S/I	
	Upfront high risk	S/III	S/III	CO/II	S/I	
	Chemosensitive relapse, prior auto-HCT	CO/II	CO/II	CO/II	S/II	GNR/III
	Refractory/relapse after three lines of prior therapy including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38					S/II
AL		CO/III	CO/III	GNR/III	CO/II	
<i>Other diseases</i>						
Acquired SAA and AA/PNH	Newly diagnosed	S/II	CO/II	GNR/III	NA	
	Relapsed/refractory	S/II	S/II	CO/II	NA	
Haemolytic PNH		GNR/II	GNR/II	GNR/II	NA	
Constitutional BMF syndromes/SAA <sup>e</sup>		S/II	S/II	CO/II	NA	
Breast Ca	Adjuvant high risk, selected population	NA	NA	NA	D/CO/I	
	Metastatic, chemosensitive	D/II	NA	NA	D/CO/II	
Germ cell tumours	Second line, high risk	GNR/III	NA	NA	CO/II	
	Primary refractory, second and further relapse	GNR/III	NA	NA	S/II	
Ovarian Ca	High risk/recurrent	GNR/II	NA	NA	GNR/I	
Medulloblastoma	Post-surgery, high risk/recurrent disease	NA	NA	NA	CO/III	
Small cell lung Ca	Limited	NA	NA	NA	GNR/I	
Soft tissue Sa	Advanced	D/III	NA	NA	D/II	
Ewing's Sa	Locally advanced/metastatic, chemosensitive	D/III	NA	NA	CO/II	
Renal cell Ca	Metastatic, refractory to conventional treatments	D/II	NA	NA	NA	
Colorectal Ca, pancreatic Ca, other selected solid tumours	Metastatic, refractory to conventional treatments	D/III	NA	NA	NA	
Multiple sclerosis	Highly active RR-MS failing DMT	D/III	GNR/III	GNR/III	S/I	
	Progressive MS with AIC, and Aggressive MS <sup>f</sup>	D/III	GNR/III	GNR/III	CO/II	
	Progressive MS without AIC	GNR/III	GNR/III	GNR/III	GNR/III	
Systemic sclerosis		D/III	GNR/III	GNR/III	S/I	
SLE		D/III	GNR/III	GNR/III	CO/II	
Crohn's disease		D/III	D/III	D/III	CO/II	
Rheumatoid arthritis		D/III	GNR/III	GNR/III	CO/II	
JIA		CO/II	CO/II	CO/III	CO/II	
Monogenic AD		CO/II	CO/II	CO/III	GNR/II	
Vasculitis	ANCA+ve, BD, Takayasu, others	GNR/III	GNR/III	GNR/III	CO/II	
PM-DM		GNR/III	GNR/III	GNR/III	CO/II	
Autoimmune cytopenias		CO/II	CO/II	CO/III	CO/II	
Neuromyelitis optica		D/III	D/III	D/III	CO/II	
CIDP, MG and SPS		GNR/III	GNR/III	GNR/III	CO/II	

**Table 2.** continued

Disease	Disease status	MSD allo	MUD allo	MMAD allo	Auto	CAR-T
Type 1 diabetes		GNR/III	GNR/III	GNR/III	D/II	
RCD type II		GNR/III	GNR/III	GNR/III	CO/II	
Primary ID		CO/II	CO/II	CO/II	NA	

This classification does not cover patients for whom a syngeneic donor is available.

AA aplastic anaemia, AD autoimmune disorders, AIC active inflammatory component, AL amyloidosis, ALL acute lymphoblastic leukaemia, Allo allogeneic transplantation, AML acute myeloid leukaemia, APL acute promyelocytic leukaemia, Auto autologous transplantation, Ca cancer or carcinoma, CAR-T chimeric antigen receptor T cells, CIDP chronic inflammatory demyelinating polyneuropathy, CLL chronic lymphocytic leukaemia, CML chronic myelogenous leukaemia, CMML chronic myelomonocytic leukaemia, CO clinical option (can be carried after careful assessment of risks and benefits), CP chronic phase, CR1, 2, 3 first, second, third complete remission, CTCL cutaneous T-cell lymphoma, D developmental (further trials are needed), DIPSS dynamic international prognostic score system, DMT disease-modifying treatments, FL follicular lymphoma, GNR generally not recommended, HL Hodgkin lymphoma, HCT haematopoietic cell transplantation, ID immunodeficiency, IPI international prognostic index, IPSS-R revised International Scoring System, JIA juvenile idiopathic arthritis, LBCL large B-cell lymphoma, MCL mantle cell lymphoma, MDS myelodysplastic syndromes, MG myasthenia gravis, MM multiple myeloma, MMAD mismatched alternative donors (cord blood, haploidentical and mismatched unrelated donors), MP-CMML myeloproliferative CMML, MRD minimal residual disease, MS multiple sclerosis, MSD matched sibling donor, MUD well-matched unrelated donor (8/8, 10/10, or 9/10 if mismatched is in DQB1), NA not applicable, PM-DM polymyositis-dermatomyositis, PNH paroxysmal nocturnal haemoglobinuria, PR partial remission, RA refractory anaemia, RAEB refractory anaemia with excess blasts, RCD refractory coeliac disease, RCMD refractory cytopenia with multilineage dysplasia, RR-MS relapsing-remitting multiple sclerosis, S standard of care (generally indicated in suitable patients), Sa sarcoma, SAA severe aplastic anaemia, sAML secondary acute myeloid leukaemia, SLE systemic lupus erythematosus, SPS stiff person syndrome, TCL T-cell lymphoma, TKI tyrosine kinase inhibitors, WM Waldenström macroglobulinemia.

<sup>a</sup>Some centres consider older age (e.g., >60 years) as a criterion for high-risk disease in decision making for allogeneic HSCT for AML or ALL. Beyond transplant indications, maintenance therapy after transplant is being increasingly used with the aim of improving survival outcomes (e.g., FLT3 inhibitors in FLT3-ITD AML [346]).

<sup>b</sup>Categories are based on number of white blood cells, cytogenetics and molecular markers at diagnosis and time to achieve remission (see text).

<sup>c</sup>Additional factors include >5% marrow blasts, poor karyotype, profound cytopenias (i.e., Hb <80 g/L, ANC <0.8 × 10<sup>9</sup>/L, platelets <50 × 10<sup>9</sup>/L), or severe BM fibrosis.

<sup>d</sup>Additional high-risk gene mutations (ASXL1, RUNX1, SETBP1, N-RAS), severe cytopenia or transfusion dependency, excessive proliferative features or extramedullary involvement.

<sup>e</sup>Constitutional SAA includes Fanconi anaemia, dyskeratosis congenita, Blackfan–Diamond anaemia and other inborn bone marrow failure syndromes (see also the section and table for paediatric indications).

<sup>f</sup>Aggressive MS as per Menon et al. [347].

Allo-HCT is also indicated for adult ALL patients in CR2 or beyond [53] and may rescue a subset of patients with resistant disease responding to novel agents such as blinatumomab, inotuzumab ozogamicin and/or CAR-T cells [54].

Anti-CD19 CAR-T cell therapy is approved for patients up to 25 years of age based on the ELIANA study [55], and more recently for adult ALL based on the ZUMA-3 trial [56]. Most trials of CAR-T cells in relapsed/refractory ALL demonstrate impressive response rates, with >70% of patients achieving CR regardless of cytogenetic background, prior therapies, or age [57]. Prognostic factors associated with higher remission rates and better outcome in adult ALL include lower disease burden (assessed by BM blast count), lower LDH and higher platelet count prior to lymphodepletion [58, 59]. TP53 mutations are associated with worse outcome [59]. Importantly, conditioning with fludarabine and cyclophosphamide is superior to cyclophosphamide alone [58]. Due to the time delay between detection of relapse and infusion of CAR-T cells, bridging therapy is often necessary, although results may be inferior in patients previously treated with blinatumomab [60] and toxicity may be higher in patients with a previous allo-HCT [59].

Relapse after CAR-T cell therapy occurs in 30–50% of patients (with CD19 negative relapse in up to 40%) [57, 61]. The question of post-CAR-T cell consolidation with allo-HCT is still open and data are controversial. Many centres undertake allo-HCT for adult ALL patients following CAR-T cell treatment even in an MRD-negative remission. In any event, patients with molecular MRD positivity following CAR-T cell therapy, loss of B-cell aplasia and without a previous HCT are candidates for consolidative allo-HCT post CAR-T cell infusion [61].

For Ph-positive ALL, allo-HCT is still indicated in CR1 [62]. Post-transplant TKIs have shown to reduce relapse rates and should therefore be considered [62]. Auto-HCT is an option for patients achieving MRD negativity [63]. However, emerging data show that patients achieving deep MRD negativity adequately treated with

TKIs in combination with mAbs may avoid HCT [64, 65]. Allo-HCT is indicated for Ph-like ALL, due to the described poor outcome irrespective of MRD status [66].

In contrast to B-ALL, salvage options in T-ALL are limited and consolidation with HCT in CR1 should be considered in high-risk patients. Similarly to B-ALL, MRD is a key predictor of relapse [7, 67]. Other high-risk features include early T-precursor immunophenotype [68] and adverse cytogenetics [69, 70]. Complex cytogenetics is associated with poor outcome, while NOTCH1 and/or FBXW7 mutations are associated with improved outcomes [67, 70].

With respect to auto-HCT, in the donor versus no donor studies and subsequent meta-analyses, no beneficial effect was observed [35–37]. The question as to whether auto-HCT should be revisited for MRD-negative patients has been discussed [63].

**Chronic myeloid leukaemia (CML).** Since the advent of TKIs, allo-HCT is not recommended as a first-line treatment in CML. In the vast majority of CML patients in chronic phase (CP), imatinib or second-generation TKIs, such as dasatinib, nilotinib or bosutinib, should be the first-line therapy. Some patients achieving molecular remission with TKI treatment have remained in molecular remission for long periods after cessation of the drug and complete discontinuation of TKI could be obtained in about 40%, but it remains to be seen in the long term whether these patients are cured [71, 72].

Patients who fail first-line therapy according to ELN guidelines should start on second-line TKI therapy. Donor search should start in patients who fail two lines of TKI. They should receive treatment with third-line TKI depending on ABL mutation analyses and are candidates to proceed to allo-HCT as soon as possible whilst in optimal response if EBMT risk score is 0–1 or, in the case of a prior loss of cytogenetic or haematological response to second-line TKI, if EBMT risk score is 0–4. If there is no haematological response to second-line treatment, patients are candidates for allo-HCT with

any EBMT risk score. Patients with ABL mutations resistant to third-generation TKI or with T315I mutation are candidates to undergo HCT with any EBMT risk score after failing second or third-line TKI.

Patients in advanced phase CML referred for an HCT could receive TKI or TKI± intensive therapy as preparation for HCT, which should be performed as soon as possible after achieving CP2 without the need for deep cytogenetic or molecular responses.

Patients with a syngeneic donor are always candidates for HCT with standard conditioning. Auto-HCT is generally not recommended outside clinical trials.

Overall, the main goal of CML therapy should be to prevent progression to the advanced phase or >CP1, as outcomes post-transplantation are worse in those situations. Patients with CML should be followed closely and considered for HCT while still in CP1 if they fulfil the criteria described above.

**Myeloproliferative neoplasms (MPNs).** Allo-HCT remains the only potential curative option for patients with MPNs. However, polycythaemia vera and essential thrombocythaemia are generally not indications for allo-HCT unless the disease has progressed to secondary myelofibrosis or secondary leukaemia [73–75]. Due to the lack of alternative therapeutic options, allo-HCT is a reasonable treatment for intermediate II and high-risk primary myelofibrosis (according to the Dynamic International Prognostic Index) [76]. In younger patients, transplantation is justified in individual cases classified as intermediate I, especially if unfavourable mutations such as EZH2 or ASXL1 or unfavourable cytogenetics are present [77, 78]. Experience of allo-HCT in patients with low-risk index disease is limited and remains controversial.

The introduction of JAK inhibitors in the treatment of primary myelofibrosis may help to improve constitutional symptoms and to reduce spleen size before HCT, but their definitive role needs to be determined [79]. Recent EBMT data suggest no disadvantage with pre-transplant exposure to ruxolitinib, and better outcomes after transplant in ruxolitinib responsive patients compared with patients with no response or loss of response to ruxolitinib [80]. A recent validated transplant risk score for myelofibrosis may be helpful in decision making [81].

Auto-HCT for MPN is generally not recommended outside clinical trials.

**Myelodysplastic syndromes (MDS).** Allo-HCT is a curative option for patients with higher-risk MDS, but patient-related factors, especially age and co-morbidities, often impact upon feasibility of HCT. EBMT proposed a transplant-specific risk score for MDS patients [82], which, along with HCT-CI, may be used to judge the feasibility of allo-HCT and predict outcomes. In addition, disease characteristics that impact the risk of transformation into AML and survival need to be considered. The revised international prognosis scoring system (IPSS-R) is the most relevant system to assess disease prognosis [83]. This revised scoring system is based on marrow blast percentage, modified cytogenetic risk groups [84] and severity of cytopenias. It is an age-adjusted risk score [85] and classifies disease-related factors in five categories of risk; 'very low' (score ≤1.5), 'low' (>1.5≤3.0), 'intermediate' (>3≤4.5), 'high' (>4≤6), and 'very high' (>6). The time to 25% AML progression/median survival in the absence of therapy were reported as follows; not reached/8.8 years, 10.8/5.3 years, 3.2/3 years, 1.4/1.6 years and 0.7/0.8 years for patients in very low-, low-, intermediate-, high- and very high- risk categories, respectively. To simplify clinical use, patients can be categorised into three risk groups when considering allo-HCT: 'lower-risk' (LR-MDS) including low- and very-low-risk groups, 'intermediate-risk', and 'higher-risk' (HR-MDS) including high- and very-high-risk groups.

While allo-HCT is a standard of care in suitably fit patients with higher-risk MDS, decision making becomes more challenging for the intermediate IPSS-R group, where patients have a median survival of 3 years without treatment and 25% AML progression at

3.2 years. Patients in the intermediate IPSS-R risk group with >5% marrow blasts at diagnosis, poor karyotype, profound cytopenias (i.e., haemoglobin <80 g/L, neutrophil count <0.8 × 10<sup>9</sup>/L, platelet count <50 × 10<sup>9</sup>/L), or severe BM fibrosis should be considered for allo-HCT. Otherwise, patients in this risk group should be offered non-transplant options as first line of therapy [83, 86].

**Chronic myelomonocytic leukaemia (CMML).** Allo-HCT represents the only potentially curative treatment option in CMML, but, due to reported high rates of TRM and post-transplant relapse, HCT is generally recommended for carefully selected patients with high-risk disease [83] and acceptable HCT-CI. However, younger patients stratified in low-risk categories may be referred for possible allo-HCT in presence of additional risk factors, such as gene mutations, severe cytopenia, transfusion dependency, excessive proliferative features or extramedullary involvement.

According to the 2016 WHO classification of myeloid neoplasms, CMML is classified in three stages: CMML-0 (blasts <5% in BM and <2% in PB, CMML-1 (blasts 5–9% in BM or 2–4% in PB) and CMML-2 (blasts 10–19% in BM or 5–19% in PB). There are two variants of the disease, 'dysplastic' and 'proliferative', depending on the circulating leukocyte count (≤13 × 10<sup>9</sup>/L and >13 × 10<sup>9</sup>/L, respectively) [87].

For the evaluation of disease-related factors, the use of a CMML-specific prognostic scoring system (CPSS) is recommended, possibly chosen among those including molecular information (CPSS-molecular, Groupe Francophone des Myelodysplasies, GFM, score, Molecular Mayo Score) [88].

Similar to MDS, and despite the absence of evidence from prospective and retrospective trials, pre-transplant treatment with hypomethylating agents or intensive chemotherapy is generally recommended for CMML-2 and CMML with severe proliferative features and/or extramedullary infiltration not controlled by conventional cytoreductive drugs, whereas upfront transplantation may be the preferred strategy for patients with low blast percentages. Recently, a 'CMML transplant score', including ASXL1 and/or NRAS-mutated genotype together with BM blasts >2% and co-morbidities, has been proposed to facilitate personalised counselling for CMML candidates for allo-HCT [89].

**Chronic lymphocytic leukaemia (CLL).** The introduction of signalling pathway inhibitors (PIs), such as the Bruton's TKI, ibrutinib, the phosphatidylinositol-3-kinase inhibitor, idelalisib, or the BCL2-inhibitor venetoclax, has changed management algorithms and HCT indications in CLL. EBMT and ERIC (European Research Initiative in CLL) have proposed a revised definition of high-risk CLL driven by TP53 abnormalities and response to treatment with PIs [90]. Patients with chemoimmunotherapy-resistant CLL but fully responsive to PI (high-risk I) should be treated with these drugs, and allo-HCT remains an option only in selected patients with a low procedure-related risk. Patients with CLL resistant to both chemoimmunotherapy and PI (high-risk II) have exhausted their main pharmacological therapeutic options and should be considered for cellular therapies, including CAR-T cells and allo-HCT, if eligible. Cellular and molecular therapies are not mutually exclusive and could be used synergistically to exploit their full potential.

Patients with CLL and a concomitant MDS and those with clonally related aggressive transformation of CLL should be considered for allo-HCT regardless of treatment stage of their CLL [91].

Auto-HCT is generally not recommended in CLL. However, it could be considered a clinical option in patients with a histological transformation clonally unrelated to CLL [92].

**Lymphomas.** Since December 2015, lymphoma patients are reported to EBMT via the mandatory MED-A as being in 'true' CR1 (first CR directly by standard first-line treatment), or as being



in 'first' CR (achieved by one or more salvage attempts after primary induction failure), clearly segregating patients with different prognoses. Therefore, the recommendations for lymphoma (in Table 2) refer to 'true' CR1 if CR1 is mentioned, and CR1 after prior refractoriness is included as CR >1, and, in some lymphoma types transplant indications in CR1 are more restrictive than in previous editions of these recommendations. In most types of lymphoma, retrospective analyses now show comparable results for MSD, MUD and haploidentical donor transplantation with PTCy (as CB and other alternative donors are used quite rarely in this setting, and are not covered by these statements). Therefore, we have now consistency across current lymphoma classifications.

**Large B-cell lymphoma (LBCL):** LBCL is defined as any entity behaving clinically similar to diffuse large B-cell lymphoma (DLBCL) regarding treatment options within the scope of this guideline, and includes peripheral mediastinal B-cell lymphoma, high-grade B-cell lymphoma NOS (not otherwise specified) and double-hit and triple-hit lymphomas.

The anti-CD19 CAR-Ts, axicabtagene ciloleucel and lisocaptogene maraleucel, show significant improvement in PFS and a strong trend in OS (significant in univariate analysis) in two Phase III clinical studies in high-risk r/r LBCL compared with salvage therapy (ST) followed by auto-HCT [93, 94]. High-risk relapse of DLBCL was defined as remission duration of <12 months after first-line therapy. By the special characteristics of the study design, chemosensitivity of the patients in the experimental arms is unknown. This urges us to introduce a new category 'untested relapse' and solely for this situation the results of CAR-T therapy are superior to those of ST followed by auto-HCT. For patients with high-risk relapsed/refractory LBCL, and unknown chemosensitivity, anti-CD19 CAR-Ts, axicabtagene ciloleucel or lisocaptogene maraleucel, will replace auto-HCT as standard of care.

In late chemosensitive relapse of LBCL after first-line therapy including rituximab, auto-HCT remains standard of care, although CAR-Ts also have to be considered for these patients. As real-world data with anti-CD19 CAR-Ts in third-line use [95] have confirmed the results of the pivotal studies [96–98], CAR-Ts are currently the standard of care in this situation.

For patients failing second-line salvage therapies, relapsing after auto-HCT or with refractory disease, allo-HCT remains a clinical option [99–103] after failure of CAR-T, although there are no robust data available yet. The curative potential of auto-HCT for double-hit lymphomas in primary treatment or thereafter is equivocal [104] and cannot be generally recommended. The recommendation for auto-HCT as consolidation after rituximab-containing first-line therapy in high-risk situations (e.g., slow responding patients to first-line therapy defined by interim PET [105]) needs further confirmation by comparative studies but has a role as a valuable clinical option.

The recommendations for primary central nervous system (CNS) lymphoma are maintained. In this DLBCL subset, there is evidence from a number of non-comparative trials and two randomised controlled trials (RCT) that consolidating auto-HCT in first remission is safe and effective, justifying categorisation as S/II [106–109]. The same holds true for synchronous nodal and CNS lymphoma in primary treatment or later [110]. In contrast, there is virtually no data on the efficacy of allo-HCT in this setting, and therefore, it is generally not recommended.

**Follicular lymphoma (FL):** In the era of therapeutic antibody maintenance, evidence for benefit of HCT in CR1 is lacking in patients with untransformed FL and in those with high-grade transformation who have not received systemic treatment for the underlying FL before the histological transformation. In contrast, consolidation with auto-HCT may be a clinical option in patients with the chemosensitive high-grade transformation

of FL, if they had received prior systemic treatment, especially immunochemotherapy. Beyond the potential efficacy of CAR-T in FL, novel drugs, such as idelalisib, have not changed the natural history of the disease, and transplant indications for FL beyond CR1 remain unchanged compared to previous editions [111, 112].

The anti-CD19 CAR-T axicabtagene ciloleucel results in a high number of durable responses in the third and higher treatment line in a non-comparative clinical trial [113]. It is therefore a clinical option in this situation. Further comparative studies are warranted to define the definite role of the treatment of FL.

**Waldenström's macroglobulinemia (lymphoplasmacytic lymphoma with IgM gammopathy; WM):** With the advent of more effective novel agents for WM, such as rituximab, purine analogues, proteasome inhibitors, and kinase inhibitors, strategies using first-line auto-HCT are increasingly questionable and are not recommended outside clinical trials [114]. Auto-HCT should be considered as a clinical option in the first relapse and for patients requiring more than one line of therapy to achieve response [115, 116]. Allo-HCT has been advocated as a clinical option for younger individuals with WM with an aggressive clinical course or high-risk disease according to the IPSS [114, 117]. Although a clear definition of aggressive WM is not formally agreed, allo-HCT might be considered in patients with short-lived responses or refractory to immunochemotherapy, proteasome-based treatment and/or kinase inhibitors.

**Mantle cell lymphoma (MCL):** Ibrutinib has been approved as an effective salvage treatment for patients with relapsed or refractory MCL. However, in the RCT setting progression-free survival of relapsed MCL is modest with ibrutinib [118]. Moreover, prognosis after ibrutinib failure appears to be extremely poor [119]. Therefore, in contrast to CLL, in MCL the advent of targeted drugs, such as ibrutinib, is yet to significantly affect the natural course of the disease and, thus, indications for HCT. However, ibrutinib might be beneficial for bridging patients with MCL to allo-HCT [120]. Studies testing ibrutinib as part of first-line therapy are ongoing. Available evidence does not suggest benefit of allo-HCT in MCL in CR1 [121]. Therefore, upfront allo-HCT in MCL outside of clinical trials is not recommended.

In a non-comparative study, the anti-CD19 CAR-T, brexucabtagene autoleucel, showed a high number of durable responses in patients failing at least two prior therapies including ibrutinib and mostly pretreated with auto-HCT [122]. The difference in terms of PFS and OS compared to other treatment modalities used in this situation as allo-HCT and the relatively low toxicity defines the medicinal product as standard of care in this situation.

**T cell lymphomas:** Peripheral T-cell lymphomas usually carry a very poor prognosis. Allo-HCT is effective in patients with relapsed and refractory disease and recommended as standard of care in patients with chemosensitive relapse, as the only curative modality in this condition. In CR1, however, a prospective randomised trial testing superiority of allo-HCT over auto-HCT was prematurely terminated due to the low likelihood of meeting its primary endpoint [123]. Thus, both auto-HCT and allo-HCT are clinical options as consolidation of first-response, but the ongoing evaluation is warranted.

Primary cutaneous T-cell lymphomas in early stage have an excellent outcome, and HCT is generally not recommended. However, patients with EORTC/ISCL advanced stages IIB to IV have a dismal prognosis with conventional therapy [124–126]. Allo-HCT offers these patients a clinically relevant and persistent graft-versus-lymphoma effect [127–129], which despite the lack of well-designed comparative trials, would suggest this to be an advantageous clinical option for these patients compared to their outcomes with only conventional therapy.

**Hodgkin lymphoma (HL):** Targeted agents such as brentuximab vedotin and checkpoint inhibitors may shift the transplant algorithms for HL in the future. For now, as in previous recommendations, auto-HCT remains standard of care for patients with relapsed HL chemosensitive to ST, and allo-HCT in those after a failed prior autograft [130–134]. CAR-Ts have been tested in the setting of prospective clinical trials; the few available results do not show convincingly better results than other treatment modalities [135]. Nodular lymphocyte predominant HL comprises only 5% of all patients being diagnosed of HL; HCT is restricted to those high-risk patients with relapsed disease [136].

**Multiple myeloma (MM).** The development of new agents, such as proteasome inhibitors, immunomodulatory drugs and mAbs, have been major advances and may eventually change the position of HCT in the treatment strategy. Currently, first-line auto-HCT is still the standard of care for newly diagnosed MM patients [137–139]. Although best results are seen in patients achieving good responses prior to HCT, some non-responding patients also benefit from this approach. Age should be considered in conjunction with general health and fitness. TBI should not be used in the conditioning regimen due to increased toxicity without appreciable benefit, and the addition of bortezomib or lenalidomide to conditioning regimens is yet to be proven to improve patient's outcome [140]. Double or 'tandem' autograft has been shown to be superior to one single auto-HCT, although the benefit of the 'second' transplant procedure (of the tandem) appears to be restricted to patients with poor risk features [141] not achieving CR or VGPR with the first transplant procedure. Immunomodulatory drugs and bortezomib as post-HCT consolidation and maintenance therapies may be an alternative option for these patients [142–145].

As the vast majority of patients still relapse after auto-HCT, the use of a further, or 'salvage' auto-HCT after re-induction therapy is an option and may be of particular benefit in patients achieving a long treatment-free interval of at least 18–24 months after the first transplant [146]. Relapse within 12 months of first auto-HCT is considered a poor risk and is not in favour of alkylator sensitivity [147].

Allo-HCT is a treatment with curative potential but associated with considerable TRM and might be used in selected high-risk patients [148]. The combination of auto-HCT followed by RIC allograft ('auto-allo') has shown a survival benefit for high-risk patients, albeit inconsistently in various clinical trials [149–152]. Recently, allo-HCT with PTCy has been shown to be feasible in MM, but relapse is still a problem [153]. Similar to the auto-HCT setting, novel agents may be complementary, and non-redundant therapies should be combined in the management of suitable allo-HCT candidates. Among patients with end-stage renal impairment, sequential allo-HCT has been reported [154].

CAR T-cell therapy has shown promising results in patients with refractory/relapsed MM [155–157]. Idecabtagene vicleucel (ABECMA™) is the first cell-based gene therapy approved by the FDA for adults with relapsed/refractory MM after four or more lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 mAb. In addition, EMA has recommended granting conditional marketing authorisation in the European Union for ABECMA™ for the treatment of adults with relapsed/refractory MM who have received at least three previous therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 mAb. Whether CAR T-cell therapy could replace auto-HCT is under investigation in randomised phase III studies (Karmma-3, NCT03651128, and Cartitude -4; NCT04181827).

**AL amyloidosis.** Patients with systemic immunoglobulin-light-chain (AL) amyloidosis without severe heart failure may benefit from auto-HCT [158]. However, the benefit was not confirmed in a

prospective randomised trial that included patients with advanced cardiac amyloidosis [159]. Many recently published studies have reported improved early mortality after an appropriate risk assessment and consistently good haematologic responses and impressive long term survival [160, 161]. Cytogenetic aberrations, as  $t(11;14)$ , can also guide therapy [162]. Allo-HCT might be considered as a clinical option in younger patients who relapsed or not responded after auto-HCT and received at least one new drug (lenalidomide or bortezomib) [163].

**Acquired severe aplastic anaemia (SAA).** HLA-identical sibling allo-HCT is considered the standard of care for adult patients with SAA, although the outcomes decline over the age of 40 [164–166]. In addition to age, careful assessment of co-morbidities prior to HCT should be made to determine fitness for upfront HCT in the age group of 35–50 years. To reduce the risk of chronic GVHD, all patients should receive in vivo T-cell depletion with ATG or alemtuzumab, and BM is the recommended source of stem cells [167–169]. The choice of conditioning regimen also depends on age; patients <30 years old should receive high-dose cyclophosphamide (200 mg/kg), and those aged 30–40 years old, a fludarabine-based regimen with lower dose cyclophosphamide (120 mg/kg). There is no indication for using radiation in the conditioning for MSD HCT.

MUD HCT can be considered as a first-line choice in young patients aged <18 years based on the excellent outcome compared to historical matched controls [170], provided transplant is feasible within the first two months after diagnosis. Alemtuzumab-based conditioning is also recommended in this situation [171]. If the interval to find a suitable MUD and proceed to HCT is predicted to be longer, then immunosuppressive therapy (IST) with ATG (preferably with horse ATG) and ciclosporin with eltrombopag is recommended in adults.

MUD HCT in young and adult patients is indicated after failure to respond to one course of IST, normally assessed at 3–6 months. Age of recipient is also an issue for MUD HCT, and along with assessment of co-morbidities and other patient and transplant characteristics (e.g., CMV status, source of cells, use of ATG, interval from diagnosis to transplant, HLA matching degree), should help in evaluating patients who would benefit most from the procedure. Classically, patients aged up to 30 years within the first year from diagnosis and refractory to immunosuppressive treatment are the best candidates for MUD HCT. Otherwise, a non-transplant approach is recommended (e.g., eltrombopag if not given first line, androgens, second course of immunosuppressive therapy) [166, 168–174]. As in MSD HCT, BM is the recommended stem cell source for MUD HCT in SAA for ATG-based conditioning regimens. Studies are ongoing to determine whether there is any preferred stem cell source for alemtuzumab-based conditioning, which provides excellent results with durable engraftment and low incidence of chronic GVHD in older (>40 years) recipients of allo-HCT for SAA from MSD or MUD.

Alternative donors for allo-HCT (e.g., CB, haploidentical or MMUD) may be considered after failure to respond to immunosuppressive therapy. Excellent results have been reported especially in young patients up to 20 years of age in the absence of MSD or MUD [175–181]. Those studies also included older patients with promising results [182, 183]. Recent data on haploidentical transplantation is promising [182, 183]. The SAAWP has approved protocols for CB and haploidentical HCT in this setting, where seeking advice from a SAA specialist centre is recommended.

Constitutional SAA and BM failure syndromes, including Fanconi anaemia (FA), dyskeratosis congenita (DKC) and other telomere diseases, may not only present in childhood but also in adults, often with more subtle clinical features. All cases of SAA being considered for HCT should have appropriate diagnostic workup, including molecular genetics, to establish or exclude constitutional BMF

syndromes, with consideration of any impact on family donors and conditioning regimen (see relevant sections below).

**Paroxysmal nocturnal hemoglobinuria (PNH).** The introduction of anti-complement therapy with eculizumab changed the natural history of the disease, and allo-HCT became generally not recommended for patients with haemolytic PNH for whom eculizumab is available. Potential indications remain dependent on the individual clinical manifestations: (i) AA/PNH syndrome, that is, PNH occurring in the presence of severe BM failure with a hypocellular BM (using the same criteria for SAA above for age, disease severity, timing of transplant, conditioning regimen and failure to respond to one course of immunosuppressive therapy in case of MUD HCT) and (ii) clonal evolution of PNH to MDS/AM [184, 185]. Patients with poor response to eculizumab who remain severely transfusion dependent may be also considered for HCT, depending on the availability of new proximal complement inhibitors. Expert advice should be sought from a PNH specialist centre.

**Solid tumours.** Currently, the EBMT Registry includes >63,000 HCT procedures in >46,000 patients with solid tumours, with >7000 procedures performed in the last 5 years. However, with the possible exception of patients with germ cell tumours (GCT), and highly-selected patients with breast cancer (BC), sarcoma and medulloblastoma, HCT is generally not recommended or developmental for most indications in solid tumours [111]. With very limited evidence published recently, the new recommendations in 2022 have changed little compared to prior indications.

Despite the encouraging role of immune surveillance and immune responses against several solid tumours [186–189] recommendations for allo-HCT, as for other forms of cellular therapy, still require further prospective trials, which should be a priority for medical oncology [190, 191].

The role of auto-HCT in BC at high-risk of recurrence and metastatic has been assessed by several randomised trials and meta-analyses of individual patient data [192, 193]. As discussed in more detail in previous reports [111, 194], the overall conclusion is that auto-HCT in BC improves PFS but not OS in most studies. However, auto-HCT may still represent a clinical option for selected patients with specific biological characteristics and/or having gross involvement of axillary nodes (adjuvant setting) or highly chemosensitive disease (advanced setting) [195–199].

In GCT, auto-HCT is a standard of care for patients with disease refractory to platinum-based chemotherapy or with a second or further relapse, a clinical option as a second line in high-risk patients, and generally not recommended as first-line therapy [200–202]. Finally, auto-HCT can be regarded as a potential clinical option in selected patients with Ewing's and soft tissue sarcomas, medulloblastoma [203–205].

Auto-HCT, being per se capable of inducing marked and rapid tumour regression, may still represent a treatment modality for selected chemosensitive solid tumours and worthy of further study in combination with effective target agents, including immunotherapy. While awaiting results of further prospective trials, the EBMT registry remains an important source to survey indications, outcome and clinical risk factors in patients with solid tumours treated with auto- and allo-HCT.

**Autoimmune diseases (AD).** Autologous and allo-HCT represent a viable therapeutic approach for many severe AD, resistant to standard therapies, after careful balance of benefits and risks [206]. Most transplant procedures for AD have been performed for multiple sclerosis (MS), followed by systemic sclerosis (SSc), currently representing the two standard indications for auto-HCT in this population [207].

Evidence is continually evolving for auto-HCT, predominantly in MS [208–212], and SSc [213–217], for which auto-HCT can be

regarded as a standard of care. There is evidence to support treatment of carefully selected patients with Crohn's disease [218, 219], systemic lupus erythematosus [220, 221], neuromyelitis optica [222, 223], chronic inflammatory demyelinating polyradiculoneuropathy [224], myasthenia gravis [225], stiff person syndrome [226, 227], systemic vasculitis (ANCA positive [228], Takayasu [229], Behçet's disease [230]) and refractory coeliac disease [231]. Altogether, available data support considering auto-HCT as an efficacious, one-off intensive therapeutic procedure for severe and refractory AD. Indeed, in the last decade better outcomes have been obtained with auto-HCT, owing to a growing centre experience in selecting the most appropriate patients to transplant paralleled by advances in conditioning and supportive care regimens, accreditation, and national socioeconomic factors [232]. Health economic reports have supported cost-effectiveness in some AD [212, 233, 234].

Despite improved survival over time, allo-HCT has remained predominantly used in younger patients [232]. According to recent EBMT registry data, this strategy can potentially provide long-term disease control in refractory AD, warranting further investigations mainly in younger patients [235]. Syngeneic HCT may be considered as an alternative to auto-HCT. Because autoimmunity can be the main, if not the only manifestation of many monogenic inborn errors of immunity, it is of primary importance to exclude such conditions before considering autologous transplantation, especially in younger adult patients with less well-defined ADs.

Multidisciplinary guidelines and recommendations for both autologous and allo-HCT, across a range of AD, have been published by the EBMT and other professional societies to support clinicians, scientists, as well as patients and carers [232, 236–243]. Recently, the EBMT has provided also updated recommendations for the best practice of HCT in AD during the COVID-19 pandemic [236].

**Inherited diseases in adults.** While HCT in inherited diseases is predominantly performed in childhood, adult patients with inherited diseases, including haemoglobinopathies, constitutional BMF syndromes and inborn errors of metabolism (IEM) and immunity (IEI) are increasingly considered for HCT [244]. The indications are the same as for inherited paediatric diseases (covered below), although presentation in adults may differ, including age of onset, course and prognosis. In some cases, access to HCT during childhood has been limited by health service resource and other non-clinical factors, necessitating consideration of HCT in adulthood.

### Transplant indications in children and adolescents

Allo-HCT in children and adolescents represents over 20% of overall allo-HCT activity, with a particular use in congenital and non-malignant diseases, many of which are rare. Transplant complications in paediatric patients impact on with the vulnerabilities of the developing child, including development-related organ dysfunction including infertility, delayed hormonal development, growth retardation and a high risk for malignancies in congenital disorders with chromosomal breakage syndromes. Improvements in high-resolution HLA matching for UD, conditioning regimens and supportive care for infectious and non-infectious complications have progressively reduced mortality and encouraged the positioning of allo-HCT particularly in non-malignant indications at an earlier stage in the course of the disease with patients in a better performance status rather than as a 'last chance for cure'. GVHD remains the major limitation for patients without optimal matched donors. New allo-HCT strategies should improve outcomes for MMAD. The updated 2022 classification of HCT procedures in children and adolescents is shown in Table 3.

**Table 3.** Proposed classification of transplant indications for children and adolescents—2022.

Disease	Disease status and subtypes	MSD allo	MUD allo	MMAD allo	Auto
<i>Haematological malignancies</i>					
AML	CR1 (low risk) <sup>a</sup>	GNR/II	GNR/II	GNR/III	GNR/II
	CR1 (high and very high risk) <sup>a</sup>	S/II	S/II	CO/II	GNR/II
	CR2	S/II	S/II	S/II	GNR/II
	>CR2	S/II	CO/II	CO/II	GNR/II
ALL	CR1 (low risk) <sup>a</sup>	GNR/II	GNR/II	GNR/III	GNR/II
	CR1 (high risk) <sup>a</sup>	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	1st CP, failing 2nd or 3rd line TKI	S/II	S/II	CO/II	GNR/III
	Accelerated phase, blast crisis or >1st CP	S/II	S/II	CO/II	GNR/III
MDS and JMML		S/II	S/II	CO/III	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, CR2	CO/II	CO/III	CO/III	S/II
<i>Non-malignant disorders and solid tumours</i>					
Primary ID	SCID	S/II	S/II	S/II	NA
	Non-SCID CID	S/II	S/II	S or CO/II	NA
	Primary HLH	S/II	S/II	S/II	NA
	Other primary ID	S/II	S/II	CO/II	NA
MPS	MPS-1H	S/II	S/II	S/II	NA
	Wolman disease <sup>b</sup>	CO/III	CO/III	CO/III	NA
	MPSII–VII <sup>b</sup>	CO/II	CO/II	CO/II	NA
	MLD	S/II	S/II	CO/II	
PSD	X-ALD	S/II	S/II	CO/II	NA
Thalassaemia and SCD		S/II	CO/II	CO/II	NA
Osteopetrosis		S/II	S/II	S/II	NA
IBMFS		S/II	S/II	CO/II	NA
Acquired SAA		S/II	S/II	CO/II	NA
Germ cell tumours		CO/II	CO/II	CO/II	CO/II
Sarcoma	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
	Osteogenic sarcoma	GNR/III	GNR/III	GNR/III	D/II
Neuroblastoma	High risk or >CR1	CO/II	CO/II	D/III	S/II
Brain tumours		GNR/III	GNR/III	GNR/III	CO/II
Wilms' tumour	>CR1	GNR/III	GNR/III	GNR/III	CO/II
AD	Including monogenic AD	CO/II	CO/II	CO/II	CO/II

This classification does not cover patients for whom a syngeneic donor is available.

*AD* autoimmune disorders, *ALL* acute lymphoblastic leukaemia, *Allo* allogeneic transplantation, *AML* acute myeloid leukaemia, *Auto* autologous transplantation, *CML* chronic myelogenous leukaemia, *CO* clinical option (can be carried after careful assessment of risks and benefits), *CR1*, 2 first, second complete remission, *D* developmental (further trials are needed), *GNR* generally not recommended, *HL* Hodgkin lymphoma, *HSCT* haematopoietic stem cell transplantation, *IBMFS* inborn marrow failure syndromes (Fanconi anaemia, dyskeratosis congenita, Blackfan–Diamond anaemia and others), *ID* immunodeficiency, *JMML* juvenile myelomonocytic leukaemia, *MDS* myelodysplastic syndromes, *MLD* metachromatic leukodystrophy, *MMAD* mismatched alternative donors (cord blood, haploidentical and mismatched unrelated donors), *MPS* mucopolysaccharidosis, *MSD* matched sibling donor, *MUD* well-matched unrelated donor (8/8, 10/10, or 9/10 if mismatched is in DQB1), *PSD* peroxisomal storage diseases, *S* standard of care (generally indicated in suitable patients), *SAA* severe aplastic anaemia, *SCD* sickle cell disease (high risk), *SCID* severe combined immunodeficiencies, *X-ALD* X-linked adrenoleukodystrophy.

<sup>a</sup>Categories are based on number of white blood cells, cytogenetics and molecular markers at diagnosis and time to achieve remission (see text).

<sup>b</sup>For Wolman disease, MPSII and VII, decision is individualised after expert evaluation.

**Acute myeloid leukaemia.** Childhood AML is a rare and heterogeneous disease, with increasing rates of cure and survival with intensive chemotherapy, particularly for patients with favourable prognostic markers. Thus, allo-HCT is not recommended as front-line therapy in low-risk patients, but remains a standard of care for patients in CR1 with high and very high-risk disease with a well-matched donor [245–248]. Alternative donors, in particular, haploidentical family members, have also an increasingly relevant role in high and very-high risk childhood AML and in patients beyond CR1 [249, 250]. Children who experience relapse of AML and reach a second CR are candidates for allo-HCT from the best available donor. Auto-HCT in this setting is generally not recommended outside prospective trials [251].

**Acute lymphoblastic leukaemia.** Allo-HCT from MSD and MUD is a standard of care for high-risk ALL patients in CR1 and in CR2 or later [252–256]. While classical risk factors have included molecular markers, chromosomal abnormalities and biological factors and resistance to initial chemotherapy [257], MRD has now become the most important prognostic factor to discriminate high- and very-high ALL risk groups [258–260]. If an MSD or an MUD cannot be identified, MMAD such as CB, MMUD, or haploidentical family donors are a clinical option [261]. In contrast to adults, stem cells from PB show no advantage in engraftment or relapse incidence compared to BM and therefore BM is the preferred stem cell source for children [262]. Most recently the FORUM trial (EudraCT: 2012-003032-22; ClinicalTrials.gov: NCT01949129), assessed in a non-inferiority study including 417 patients the role of TBI in ALL. Surprisingly, in the intention-to-treat population, the 2-year OS was significantly higher following TBI versus chemotherapy-only conditioning. Two-year cumulative incidence of relapse and TRM were 0.12 and 0.02 following TBI and 0.33 and 0.09 following chemotherapy-only conditioning, respectively. This trial ‘regrettably’ showed that improved OS and lower relapse risk were observed following TBI plus etoposide compared with chemotherapy-only conditioning. At this point in time, TBI plus etoposide must be recommended for patients >4 years old with high-risk ALL undergoing allo-HCT [263].

**Chronic myeloid leukaemia.** As discussed earlier for adult patients, since the advent of TKI, allo-HCT is not recommended as a first-line treatment of CML in children and adolescents either. However, it remains a standard option for patients with treatment failure, recurrence after receiving salvage second-generation TKI treatment and advanced phase CML [264–266]. Of particular relevance for paediatric patients, the indication for allo-HCT needs careful individual consideration to balance the well-established long-term complications of HCT with adverse events from prolonged TKI treatment, which may include growth failure, hepatic, and cardiac complications [267–269]. Stronger evidence from prospective cooperative studies is needed to address disease evolution after TKI discontinuation and other issues specifically in paediatric patients with CML [265, 270].

**Myelodysplastic syndromes and juvenile myelomonocytic leukaemia.** Allo-HCT from a MSD or a MUD is the treatment of choice for children with primary MDS including juvenile myelomonocytic leukaemia, as well as secondary AML [271–273]. Auto-HCT is not recommended outside clinical trials.

**Lymphoma.** Nearly all children and adolescents with Hodgkin and non-Hodgkin lymphoma are cured with multidrug chemotherapy. Few such paediatric patients are eligible for HCT (Table 3) [274–278], but include patients with residual disease after re-induction therapy of contemporary chemotherapy-protocols, patients with early NHL-relapses or patients with inadequate response or relapse of ALK-positive anaplastic large cell

lymphoma. All other approaches should be discussed with experts in the front-line chemotherapy trials.

**Solid tumours.** Although the published results have not proven yet an unequivocal benefit for most indications, children and adolescents with solid tumours can undergo auto-HCT following high-dose chemotherapy as a clinical option or within research protocols, preferably as part of first-line treatment strategies (Table 3). 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-HCT has been demonstrated by randomised trials [279, 280]. In general, allo-HCT in children with solid tumours should only be explored within prospective clinical trials in highly experienced centres.

**Acquired severe aplastic anaemia.** Allo-HCT from an MSD is the standard front-line therapy for children with acquired SAA. In patients without an MSD, a well-matched unrelated HCT is now also considered a standard front-line therapy in many patients if the donor is readily available, and the search should in any case be initiated before starting any immunosuppressive therapy [281–285]. For those who fail their first course of immunosuppression, if a well-matched UD is identified, the transplant or the second course of immunosuppression should be given, according to clinical status.

**Autoimmune diseases.** Autologous and allo-HCT may be considered a clinical option for children and adolescents with AD [206, 232, 236]. Overall, given the overlap between autoimmune, auto-inflammatory and inborn errors of immunity in the paediatric age group, there should be appropriate specialist expertise in diagnostics (such as NGS, WGS/exome sequencing) and appraising alternative treatment options in the selection of patients for HCT. Special consideration should be given to AD that remains refractory to several lines of conventional and disease-modifying treatments for which an allo-HCT might be appropriate as the ultimate chance for disease control and cure [235].

Auto-HCT may be considered for carefully selected subpopulations of patients with juvenile inflammatory arthritis (e.g., polyarticular course or onset, inadequate response and/or intolerance to prednisone or disease-modifying antirheumatic drugs) and other ADs including systemic sclerosis, systemic lupus erythematosus, vasculitis and polymyositis-dermatomyositis. Paediatric multiple sclerosis is a rare indication of auto-HCT, and long-term responses have been reported [286].

Crohn’s disease is a potential indication for auto-HCT. However, there should be careful consideration of monogenic forms of inflammatory bowel disease (e.g., IL-10 signalling defects, immunodysregulation polyendocrinopathy enteropathy X-linked—IPEX [287]—syndrome, Wiskott–Aldrich syndrome or increasingly X-linked inhibitor of apoptosis—XIAP-deficiency) [240], which are IEI for which allo-HCT is appropriate.

Auto-HCT and allo-HCT have both been performed in severe autoimmune cytopenias, with similar outcomes [288]. Allo-HCT may also result in long-term responses in severe juvenile inflammatory arthritis [289]. A recent retrospective EBMT study reported the long-term outcome of allo-HCT in various haematological and non-haematological severe AD, including also paediatric patients [235]. Better transplant outcomes have been reported for age <18 years, and more recent years of transplant.

**Inherited diseases.** Allo-HCT for inherited diseases features predominantly in the paediatric and TYA group, but occasionally older patients require consideration and treatment. In recent years, genetically modified autologous HCT has become available in some diseases, although detailed appraisal is beyond the scope of these recommendations.

**Constitutional bone marrow failure syndromes:** Allo-HCT is the only treatment able to restore normal haematopoiesis in these patients. Transfusion-dependent FA patients with a suitably well-matched family or UD should be transplanted while in the phase of moderate cytopenia with no poor-risk clonal abnormalities and no MDS/AML [290–292]. For patients who lack a well-matched donor, HCT from MMAD should be considered as a clinical option in the context of a clinical protocol. Although outcomes are reported to be better at age <10 years, this is not the only criterion for decision making. Details on transplant conditioning for particular indications are beyond the scope of these recommendations, but it is important that standard doses of chemotherapy and/or irradiation are absolutely avoided in HCT for FA due to the underlying defect in DNA repair. Although radiation-free regimens including busulfan, cyclophosphamide, fludarabine, ATG with the infusion of a T-cell-depleted graft provide excellent outcomes in HCT from allogeneic donors other than MSD [292], the addition of low-dose irradiation may be indicated for those patients with clonal evolution or receiving transplantation from a UD due to a higher risk of graft rejection. In addition, MSD must be tested for chromosomal fragility, given that some FA subjects can have nearly normal somatic and haematological phenotype. BM is recommended above PB as HSC source, as PB is an independent risk factor for second malignancies.

Patients with DKC and other inherited BMF syndromes should be transplanted if they have a MSD or a MUD [293–295]. A recent large retrospective SAAWP study on allo-HCT for DKC and other telomeropathies showed that pre-transplant organ damage (lung and liver) was associated with poorer outcome [293], supporting thorough organ assessment before HCT. RIC regimens incorporating fludarabine are currently recommended [294, 295]. Potential sibling donors should be tested for telomere length and for mutations of gene of the telomerase-shelterin complex to rule out alterations despite normal somatic and haematologic phenotype.

Patients with Blackfan–Diamond anaemia with a MSD should be transplanted if they do not respond to steroids. If a MSD is not available, allo-HCT may be performed with a MUD in experienced centres [296].

Discussion with a specialist centre is advised regarding possible HCT in patients with constitutional BMF.

**Inborn errors of immunity (IEI):** IEIs are a large group of >450 genetic diseases characterised by a variable susceptibility to infections and/or immune dysregulation related manifestations such as autoimmunity and autoinflammation [297]. Chronic benign or malignant lymphoproliferation, frequently driven by persistent viral infections can occur and the incidence of malignancies is also increased. Allo-HCT is curative for adaptive immune defects and for selected innate immune deficiencies. Indication and modalities including timing of HCT are highly variable depending on the disease [298]. The decision to proceed with allo-HCT is straightforward in certain conditions such as severe combined immunodeficiencies (SCID) and primary hemophagocytic lymphohistiocytosis (HLH), while for other diseases the final decision can be challenging and depends on a combination of factors, such as immunological parameters, severity of clinical manifestations, organ damage (present or anticipated) and availability of a suitable donor. If the molecular diagnosis is known, insight into the natural history of the disease can help even though a strict genotype/phenotype correlation is often absent. In any case, a careful multidisciplinary evaluation of each individual patient by teams with experience in the care of IEIs is mandatory to tailor the best treatment and guide the patient to HCT with the appropriate timing.

IEIs affecting T-cell immunity with abnormal development and/or function are the most severe and allo-HCT is frequently indicated. SCID is the most severe disease category and leads to an early death unless HCT or in certain circumstances gene therapy, is offered early in life.

Non-SCID-T cell deficiencies are numerous and responsible for a broad variability of symptoms and severity. In the most severe conditions such as MHC class II deficiency [299] Wiskott–Aldrich syndrome, DOCK8 deficiency [300], CD40 ligand deficiency [301], CD27/70 deficiency [302] and a growing number of related diseases allo-HCT has to be strongly considered early in life, particularly if an HLA-matched donor is available. Progress in haploidentical transplants thanks to selective depletion of the graft (such as TCRab/CD19) [303–305] or T-replete graft with PTCy further enlarge indications in selected cases [306, 307].

An increasing number of diseases known as primary immune regulation disorders have been identified. These conditions are treatable with allo-HCT but decision and timing of the transplant are challenging. Control of inflammatory features before transplantation is important [308].

Primary HLH, regardless of the underlying genetic cause is an unambiguous indication for HCT, including with alternative donors. Disease remission prior to allo-HCT is a key factor influencing OS. Pre-emptive HCT, before the manifestation of any HLH-related symptoms, can be discussed in selected cases [309, 310]. Among innate immune defects, complete leukocyte adhesion deficiency has a straightforward indication of HCT [311]. In chronic granulomatous disease, improvement of outcome after HCT allows us to enlarge the HCT indication in particular when an HLA-matched donor is available [312].

Stem cell gene therapy has been pioneered in X-linked and ADA-SCID, leading to EMA licensing of gammaretroviral product Strimvelis®, while excellent results have recently been reported with a lentivirus-based approach [313]. The most recent lentiviral gene therapy studies in other IEI have provided encouraging results and positioning of this alternative curative treatment option is expected in the next years [314, 315].

**Inborn errors of metabolism (IEM):** Allo-HCT is effective in well-selected patients with peroxisomal diseases (PSD), lysosomal storage diseases (LSD), and some other IEM disorders [316]. Among LSD, success of this approach is best exemplified in type I mucopolysaccharidosis (or Hurler's syndrome), a severe multi-systemic disease with progressive neurocognitive involvement. Engraftment of donor-derived myeloid cells, including microglia, provides the missing enzyme to the recipient. Early intervention (before the age of 2 years), with HCT from a wild-type donor (heterozygous carriers will provide less enzyme), with tailored busulfan-based conditioning regimen to reach full donor chimerism gives the best outcome. CB and BM are both eligible as HSC source. HCT will attenuate but not erase long-term disease manifestations.

In metachromatic leukodystrophy (MLD), a central and peripheral demyelinating disease, allo-HCT is ineffective in early infantile disease but may have an impact in attenuating juvenile and adult forms when applied early in the disease course. Allo-HCT also has a role in other LSD, such as MPSII, MPSVII and Wolman disease. Given the rarity, expert MDT assessment of individual cases is essential.

Among PSD, allo-HCT is effective at preventing disease progression in the childhood, or rarely adult, presentation of cerebral inflammatory disease of X-linked adrenoleukodystrophy (X-ALD). Not all males within kindreds are affected, and allo-HCT should not be offered to those with advanced disease, as it further likely has no impact on other disease manifestations including the later development of myelopathy. Typically, genetically affected males are screened with serial MR imaging and transplant is offered at the earliest sign of disease.

Mitochondrial neurogastrointestinal encephalomyopathy is a rare multisystem disorder caused by mutations in thymidine phosphorylase [317]. Allo-HCT provides the deficient enzyme and prevents further accumulation of toxic substrate responsible for disease manifestations, and progression of the disease. Allo-HCT is

often challenging, but considered 'standard' in correctly selected clinical cases.

Gene therapy from gene-corrected autologous HSC is very promising in IEM through providing supra-physiologic enzyme production. This is now established therapy in late infantile MLD and trials are in progress in MPSIIH and MPSIIIA [318]. Lentiviral GT product have also been recently licensed by EMA in X-ALD [319]. However, careful clinical case selection is needed.

**Haemoglobinopathies:** Allo-HCT from a healthy MSD or a related CB represents the treatment of choice for young patients with transfusion-dependent  $\beta$ -thalassaemia (TDT). For patients without an MSD, a transplant from a MUD is a clinical option [320–324].

Li et al. [325] showed in TDT that MSD and MUD produce overlapping OS and event-free survival curves so that these donor choices are equivalent, similar to malignant diseases. Although the outcome of haploidentical HCT was inferior in the Li trial, it was probably biased as age is a significant denominator and the value of haploidentical HCT needs to be tested in a controlled stratified trial. HCT in TDT from haploidentical related donors is now increasingly performed as a clinical option in experienced centres [326–328].

The situation in sickle cell disease (SCD) is slightly different to TDT. The mortality of infants and small children with SCD has reduced significantly with simple measures of conventional therapy such as vaccination, antibiotic treatment, parent education and the use of hydroxyurea starting in infancy. Nevertheless, adult mortality has only shifted to older ages as conventional therapies do not have an impact on progressive organ damage. Therefore, adults continue to succumb to heart, pulmonary, renal failure and stroke, and remain often disabled many years prior to these terminal events. For this reason, allo-HCT from a MSD is standard of care and should be offered prior to the emergence of serious complications [329–331].

In SCD, age is a significant denominator for outcome since the incidence of acute and, more significantly, chronic GVHD reaches 17 and 20%, respectively, following HCT from a MSD in patients beyond 15 years [332]. The general theme that MSD and MUD produce overlapping OS and event-free survival is not reproducible in SCD where HCT from MUD is inferior to MSD with a major decline in outcome in patients beyond 13 years [333].

In SCD, MSD/MUD donor availability is below 20%. Recent reports demonstrated successful outcomes with haploidentical transplantation [334, 335] and alternative donors are considered a clinical option using either PTcY or T-cell-depleted strategies.

Since SCD is mainly a systemic vasculopathy with unexpected and disease-specific complications during allo-HCT such as PRES, macrophage activation syndrome, significant pain crises during HCT and organ failure, experimental approaches should only be performed in controlled clinical trials in highly experienced centres [334].

CRISPR-Cas9 gene-editing approaches are currently evaluated in Phase I trials as potential alternatives to allo-HCT [336]. Lentiviral-based gene therapy approach for beta-thalassaemia and SCD have received market authorisation but are not available in Europe.

Importantly, HCT for hemoglobinopathies should be performed early in life to reduce complications, in particular the incidence of chronic GVHD. Delay may also lead to irreversible damage due to iron overload in patients with TDT and systemic vasculopathy in patients with SCD.

**Osteopetrosis (OP):** OP is a heterogeneous genetic disease related to several gene defects affecting osteoclast function and characterised by impaired bone resorption. Bone density is increased on X-ray. Classical infantile OP leads to early manifestations such as macrocrania, vision impairment, haematological insufficiency, hepatosplenomegaly and hypocalcemia. Urgent HCT is indicated after exclusion of neurodegenerative and osteoclast-extrinsic defects. Atypical, delayed disease may occur, for whom

HCT may be considered in case of haematological insufficiency or imminent visual impairment [337].

### QUALITY IN HCT: JACIE AND EBMT BENCHMARKING

Currently, the JACIE standards, produced in collaboration with the Foundation for the Accreditation of Cellular Therapy (FACT), are in their 8th edition and have been expanded to incorporate immune effector and other cell and gene therapies, such as CAR-T cells. JACIE has been increasingly recognised by governmental bodies and competent authorities in several EU member states and extends beyond Europe with accredited centres worldwide. Importantly, JACIE accreditation appears to have an impact on survival outcomes and donor safety [232, 338–344]. During the pandemic, JACIE supported self-assessment by centres to help maintain minimum quality standards in the midst of the challenges faced by health services. How JACIE adapts to the post-pandemic situation is an area for active consideration with greater use of remote inspections, self-assessments and other practicable ways of working.

In terms of ongoing developments, JACIE and the EBMT Registry have delivered the first two pilot phases of a risk-adapted benchmarking system that takes into consideration the heterogeneity of the disease, patient and transplant characteristics. This will enable EBMT member centres to benchmark their survival outcomes against national and/or international norms, irrespective of the size of their HCT community, and potentially this could apply to individual indications to provide 'real-world' estimates and benchmarking of survival at international, national or centre level and comparison with non-transplant alternatives [345].

### CONCLUSIONS

For over two decades, the EBMT indications reports have incorporated developments in HCT practice based on scientific and technical developments in HCT. We encourage harmonisation of practice, where possible, to ensure meaningfully aggregated experience across indications via registry outputs. We also recommend working according to JACIE accreditation standards benchmarking of outcomes to maintain quality in HCT practice.

Moving forward, all treatment decisions, whether HCT or non-HCT, need to accommodate the ongoing COVID-19 pandemic. Although the full impact of the pandemic is yet to be determined, our understanding and evidence-base is evolving in combination with public health measures, vaccination strategies and new treatments in the HCT population. We therefore recommend that decision making across indications is delivered within the MDT with reference to EBMT and other national guidance in relation to COVID-19, and in accordance with current local conditions.

### REFERENCES

1. Duarte RF, Labopin M, Bader P, Basak GW, Chiara B, Chabannon C, et al. Indications for haematopoietic stem cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2019. *Bone Marrow Transplant.* 2019;54:1525–52.
2. Passweg JR, Baldomero H, Chabannon C, Corbacioglu S, de la Cámara R, Dolstra H, et al. Impact of the SARS-CoV-2 pandemic on hematopoietic cell transplantation and cellular therapies in Europe 2020. A report from the EBMT activity survey. *Bone Marrow Transplant.* 2022:1–11.
3. Weisdorf D, Spellman S, Haagenson M, Horowitz M, Lee S, Anasetti C, et al. Classification of HLA-matching for retrospective analysis of unrelated donor transplantation: revised definitions to predict survival. *Biol Blood Marrow Transplant.* 2008;14:748–58.
4. Weisdorf D, Cooley S, Wang T, Trachtenberg E, Haagenson MD, Vierra-Green C, et al. KIR donor selection: feasibility in identifying better donors. *Biol Blood Marrow Transplant.* 2019;25:e28–e32.
5. Gooptu M, Romee R, St Martin A, Arora M, Al Malki M, Antin JH, et al. HLA-haploidentical vs matched unrelated donor transplants with posttransplant cyclophosphamide-based prophylaxis. *Blood.* 2021;138:273–82.

6. Sanz J, Galimard JA, Labopin M, Afanasyev B, Angelucci E, Ciceri F, et al. Post-transplant cyclophosphamide after matched sibling, unrelated and haploidentical donor transplants in patients with acute myeloid leukemia: a comparative study of the ALWP EBMT. *J Hematol Oncol.* 2020;13:46.
7. Sanz J, Galimard JE, Labopin M, Afanasyev B, Sergeevich MI, Angelucci E, et al. Post-transplant cyclophosphamide containing regimens after matched sibling, matched unrelated and haploidentical donor transplants in patients with acute lymphoblastic leukemia in first complete remission, a comparative study of the ALWP of the EBMT. *J Hematol Oncol.* 2021;14:84.
8. Martínez C, Gayoso J, Canals C, Finel H, Peggs K, Dominiotto A, et al. Post-transplantation cyclophosphamide-based haploidentical transplantation as alternative to matched sibling or unrelated donor transplantation for hodgkin lymphoma: a registry study of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. *J Clin Oncol.* 2017;35:3425–32.
9. Dreger P, Sureda A, Ahn KW, Eapen M, Litovich C, Finel H, et al. PTCy-based haploidentical vs matched related or unrelated donor reduced-intensity conditioning transplant for DLBCL. *Blood Adv.* 2019;3:360–9.
10. Battipaglia G, Galimard JE, Labopin M, Raiola AM, Blaise D, Ruggeri A, et al. Post-transplant cyclophosphamide in one-antigen mismatched unrelated donor transplantation versus haploidentical transplantation in acute myeloid leukemia: a study from the Acute Leukemia Working Party of the EBMT. *Bone Marrow Transplant.* 2022;57:562–71.
11. Shouval R, Fein JA, Shouval A, Danylesko I, Shem-Tov N, Zlotnik M, et al. External validation and comparison of multiple prognostic scores in allogeneic hematopoietic stem cell transplantation. *Blood Adv.* 2019;3:1881–90.
12. Shouval R, Fein JA, Labopin M, Cho C, Bazarbachi A, Baron F, et al. Development and validation of a disease risk stratification system for patients with haematological malignancies: a retrospective cohort study of the European Society for Blood and Marrow Transplantation registry. *Lancet Haematol.* 2021;8:e205–e15.
13. McDonald GB, Sandmaier BM, Mielcarek M, Sorror M, Pergam SA, Cheng GS, et al. Survival, nonrelapse mortality, and relapse-related mortality after allogeneic hematopoietic cell transplantation: comparing 2003–2007 versus 2013–2017 cohorts. *Ann Intern Med.* 2020;172:229–39.
14. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017;129:424–47.
15. Canaani J, Labopin M, Itälä-Remes M, Blaise D, Socié G, Forcade E, et al. Prognostic significance of recurring chromosomal abnormalities in transplanted patients with acute myeloid leukemia. *Leukemia.* 2019;33:1944–52.
16. Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, et al. Genomic classification and prognosis in acute myeloid leukemia. *N Engl J Med.* 2016;374:2209–21.
17. Cornelissen JJ, Blaise D. Hematopoietic stem cell transplantation for patients with AML in first complete remission. *Blood.* 2016;127:62–70.
18. Moarii M, Papaemmanuil E. Classification and risk assessment in AML: integrating cytogenetics and molecular profiling. *Hematol Am Soc Hematol Educ Program.* 2017;2017:37–44.
19. Kantarjian H, Kadia T, DiNardo C, Daver N, Borthakur G, Jabbour E, et al. Acute myeloid leukemia: current progress and future directions. *Blood Cancer J.* 2021;11:41.
20. Araki D, Wood BL, Othus M, Radich JP, Halpern AB, Zhou Y, et al. Allogeneic hematopoietic cell transplantation for acute myeloid leukemia: time to move toward a minimal residual disease-based definition of complete remission? *J Clin Oncol.* 2016;34:329–36.
21. Kim HJ, Kim Y, Kang D, Kim HS, Lee JM, Kim M, et al. Prognostic value of measurable residual disease monitoring by next-generation sequencing before and after allogeneic hematopoietic cell transplantation in acute myeloid leukemia. *Blood Cancer J.* 2021;11:109.
22. Fenwarth L, Thomas X, de Botton S, Duployez N, Bourhis JH, Lesieur A, et al. A personalized approach to guide allogeneic stem cell transplantation in younger adults with acute myeloid leukemia. *Blood.* 2021;137:524–32.
23. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allo-HCT. *Blood.* 2005;106:2912–9.
24. Shouval R, Labopin M, Bondi O, Mishan-Shamay H, Shimoni A, Ciceri F, et al. Prediction of allogeneic hematopoietic stem-cell transplantation mortality 100 days after transplantation using a machine learning algorithm: a European Group for Blood and Marrow Transplantation Acute Leukemia Working Party Retrospective Data Mining Study. *J Clin Oncol.* 2015;33:3144–51.
25. Ringdén O, Boumendil A, Labopin M, Canaani J, Beelen D, Ehninger G, et al. Outcome of allogeneic hematopoietic stem cell transplantation in patients age >69 years with acute myelogenous leukemia: on behalf of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* 2019;25:1975–83.
26. Nagler A, Savani BN, Labopin M, Polge E, Passweg J, Finke J, et al. Outcomes after use of two standard ablative regimens in patients with refractory acute myeloid leukaemia: a retrospective, multicentre, registry analysis. *Lancet Haematol.* 2015;2:e384–92.
27. Gilleece MH, Labopin M, Savani BN, Yakoub-Agha I, Socié G, Gedde-Dahl T, et al. Allogeneic haemopoietic transplantation for acute myeloid leukaemia in second complete remission: a registry report by the Acute Leukaemia Working Party of the EBMT. *Leukemia.* 2020;34:87–99.
28. Schetelig J, Schaich M, Schäfer-Eckart K, Hänel M, Aulitzky WE, Einsele H, et al. Hematopoietic cell transplantation in patients with intermediate and high-risk AML: results from the randomized Study Alliance Leukemia (SAL) AML 2003 trial. *Leukemia.* 2015;29:1060–8.
29. Rücker FG, Agrawal M, Corbacioglu A, Weber D, Kapp-Schwoerer S, Gaidzik VI, et al. Measurable residual disease monitoring in acute myeloid leukemia with t(8;21)(q22;q22.1): results from the AML Study Group. *Blood.* 2019;134:1608–18.
30. Jourdan E, Boissel N, Chevret S, Delabesse E, Renneville A, Comillet P, et al. Prospective evaluation of gene mutations and minimal residual disease in patients with core binding factor acute myeloid leukemia. *Blood.* 2013;121:2213–23.
31. Ivey A, Hills RK, Simpson MA, Jovanovic JV, Gilkes A, Grech A, et al. Assessment of minimal residual disease in standard-risk AML. *N Engl J Med.* 2016;374:422–33.
32. Freeman SD, Hills RK, Virgo P, Khan N, Couzens S, Dillon R, et al. Measurable residual disease at induction redefines partial response in acute myeloid leukemia and stratifies outcomes in patients at standard risk without NPM1 mutations. *J Clin Oncol.* 2018;36:1486–97.
33. Giebel S, Boumendil A, Labopin M, Seesagur A, Baron F, Ciceri F, et al. Trends in the use of hematopoietic stem cell transplantation for adults with acute lymphoblastic leukemia in Europe: a report from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). *Ann Hematol.* 2019;98:2389–98.
34. Bassan R, Bourquin JP, DeAngelo DJ, Chiaretti S. New approaches to the management of adult acute lymphoblastic leukemia. *J Clin Oncol.* 2018;JCO2017773648.
35. Giebel S, Marks DI, Boissel N, Baron F, Chiaretti S, Ciceri F, et al. Hematopoietic stem cell transplantation for adults with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission: a position statement of the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL) and the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant.* 2019;54:798–809.
36. Gupta V, Richards S, Rowe J. Allogeneic, but not autologous, hematopoietic cell transplantation improves survival only among younger adults with acute lymphoblastic leukemia in first remission: an individual patient data meta-analysis. *Blood.* 2013;121:339–50.
37. Pidala J, Djulbegovic B, Anasetti C, Kharfan-Dabaja M, Kumar A. Allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia (ALL) in first complete remission. *Cochrane Database Syst Rev.* 2011;2011:Cd008818.
38. Dhédin N, Huynh A, Maury S, Tabrizi R, Beldjord K, Asnafi V, et al. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. *Blood.* 2015;125:2486–96. quiz 2586
39. Giebel S, Labopin M, Socié G, Beelen D, Browne P, Volin L, et al. Improving results of allogeneic hematopoietic cell transplantation for adults with acute lymphoblastic leukemia in first complete remission: an analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Haematologica.* 2017;102:139–49.
40. Nagler A, Labopin M, Koc Y, Angelucci E, Fischer J, Arat M, et al. Outcome of T-cell-replete haploidentical stem cell transplantation improves with time in adults with acute lymphoblastic leukemia: A study from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Cancer.* 2021;127:2507–14.
41. Malard F, Mohty M. Acute lymphoblastic leukaemia. *Lancet.* 2020;395:1146–62.
42. Short NJ, Kantarjian H, Jabbour E. Optimizing the treatment of acute lymphoblastic leukemia in younger and older adults: new drugs and evolving paradigms. *Leukemia.* 2021;35:3044–58.
43. Muffly L, Kebriaei P. Philadelphia chromosome positive acute lymphoblastic leukemia in adults: therapeutic options and dilemmas in 2020. *Semin Hematol.* 2020;57:137–41.
44. Harris K, LaBelle JL, Bishop MR. Current status of CAR T cell therapy for leukemias. *Curr Treat Options Oncol.* 2021;22:62.
45. Pavlů J, Labopin M, Niittyvuopio R, Socié G, Yakoub-Agha I, Wu D, et al. Measurable residual disease at myeloablative allogeneic transplantation in adults with acute lymphoblastic leukemia: a retrospective registry study on 2780 patients from the acute leukemia working party of the EBMT. *J Hematol Oncol.* 2019;12:108.
46. Stock W, Luger SM, Advani AS, Yin J, Harvey RC, Mullighan CG, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: results of CALGB 10403. *Blood.* 2019;133:1548–59.



47. Gökbuğet N, Kneba M, Raff T, Trautmann H, Bartram CR, Arnold R, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. *Blood*. 2012;120:1868–76.
48. Bassan R, Spinelli O, Oldani E, Intermesoli T, Tosi M, Peruta B, et al. Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL). *Blood*. 2009;113:4153–62.
49. Ribera JM, Oriol A, Morgades M, Montesinos P, Sarrà J, González-Campos J, et al. Treatment of high-risk Philadelphia chromosome-negative acute lymphoblastic leukemia in adolescents and adults according to early cytologic response and minimal residual disease after consolidation assessed by flow cytometry: final results of the PETHEMA ALL-AR-03 trial. *J Clin Oncol*. 2014;32:1595–604.
50. Moorman AV, Harrison CJ, Buck GA, Richards SM, Secker-Walker LM, Martineau M, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. *Blood*. 2007;109:3189–97.
51. Pullarkat V, Slovak ML, Kopecky KJ, Forman SJ, Appelbaum FR. Impact of cytogenetics on the outcome of adult acute lymphoblastic leukemia: results of Southwest Oncology Group 9400 study. *Blood*. 2008;111:2563–72.
52. Lazaryan A, Dolan M, Zhang MJ, Wang HL, Kharfan-Dabaja MA, Marks DI, et al. Impact of cytogenetic abnormalities on outcomes of adult Philadelphia-negative acute lymphoblastic leukemia after allogeneic hematopoietic stem cell transplantation: a study by the Acute Leukemia Working Committee of the Center for International Blood and Marrow Transplant Research. *Haematologica*. 2021;106:2295–6.
53. Brissot E, Labopin M, Russo D, Martin S, Schmid C, Glass B, et al. Alternative donors provide comparable results to matched unrelated donors in patients with acute lymphoblastic leukemia undergoing allogeneic stem cell transplantation in second complete remission: a report from the EBMT Acute Leukemia Working Party. *Bone Marrow Transplant*. 2020;55:1763–72.
54. Pavlů J, Labopin M, Zoellner AK, Sakellari I, Stelljes M, Finke J, et al. Allogeneic hematopoietic cell transplantation for primary refractory acute lymphoblastic leukemia: a report from the Acute Leukemia Working Party of the EBMT. *Cancer*. 2017;123:1965–70.
55. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378:439–48.
56. Shah BD, Ghobadi A, Oluwole OO, Logan AC, Boissel N, Cassaday RD, et al. KTE-X19 for relapsed or refractory adult B-cell acute lymphoblastic leukaemia: phase 2 results of the single-arm, open-label, multicentre ZUMA-3 study. *Lancet*. 2021;398:491–502.
57. Mohty M, Gautier J, Malard F, Aljurf M, Bazarbachi A, Chabannon C, et al. CD19 chimeric antigen receptor-T cells in B-cell leukemia and lymphoma: current status and perspectives. *Leukemia*. 2019;33:2767–78.
58. Hay KA, Gauthier J, Hirayama AV, Voutsinas JM, Wu Q, Li D, et al. Factors associated with durable EFS in adult B-cell ALL patients achieving MRD-negative CR after CD19 CAR T-cell therapy. *Blood*. 2019;133:1652–63.
59. Zhang X, Lu XA, Yang J, Zhang G, Li J, Song L, et al. Efficacy and safety of anti-CD19 CAR T-cell therapy in 110 patients with B-cell acute lymphoblastic leukemia with high-risk features. *Blood Adv*. 2020;4:2325–38.
60. Pillai V, Muralidharan K, Meng W, Bagashev A, Oldridge DA, Rosenthal J, et al. CAR T-cell therapy is effective for CD19-dim B-lymphoblastic leukemia but is impacted by prior blinatumomab therapy. *Blood Adv*. 2019;3:3539–49.
61. Dholaria B, Savani BN, Huang XJ, Nagler A, Perales MA, Mohty M. The evolving role of allogeneic hematopoietic cell transplantation in the era of chimeric antigen receptor T-cell therapy. *Br J Haematol*. 2021;193:1060–75.
62. Brissot E, Labopin M, Beckers MM, Socié G, Rambaldi A, Volin L, et al. Tyrosine kinase inhibitors improve long-term outcome of allogeneic hematopoietic stem cell transplantation for adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia. *Haematologica*. 2015;100:392–9.
63. Gorin NC, Giebel S, Labopin M, Savani BN, Mohty M, Nagler A. Autologous stem cell transplantation for adult acute leukemia in 2015: time to rethink? Present status and future prospects. *Bone Marrow Transplant*. 2015;50:1495–502.
64. Jabbour E, Short NJ, Ravandi F, Huang X, Daver N, DiNardo CD, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: long-term follow-up of a single-centre, phase 2 study. *Lancet Haematol*. 2018;5:e618–e27.
65. Foà R, Bassan R, Vitale A, Elia L, Piciocchi A, Puzolo MC, et al. Dasatinib-blinatumomab for Ph-positive acute lymphoblastic leukemia in adults. *N Engl J Med* 2020;383:1613–23.
66. Jain N, Roberts KG, Jabbour E, Patel K, Eterovic AK, Chen K, et al. Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults. *Blood*. 2017;129:572–81.
67. Marks DI, Paietta EM, Moorman AV, Richards SM, Buck G, DeWald G, et al. T-cell acute lymphoblastic leukemia in adults: clinical features, immunophenotype, cytogenetics, and outcome from the large randomized prospective trial (UKALL XII/ECOG 2993). *Blood*. 2009;114:5136–45.
68. Jain N, Lamb AV, O'Brien S, Ravandi F, Konopleva M, Jabbour E, et al. Early T-cell precursor acute lymphoblastic leukemia/lymphoma (ETP-ALL/LBL) in adolescents and adults: a high-risk subtype. *Blood*. 2016;127:1863–9.
69. Petit A, Trinquand A, Chevret S, Ballerini P, Cayuela JM, Gardel N, et al. Oncogenetic mutations combined with MRD improve outcome prediction in pediatric T-cell acute lymphoblastic leukemia. *Blood*. 2018;131:289–300.
70. Asnafi V, Buzyn A, Le Noir S, Baleydiere F, Simon A, Beldjord K, et al. NOTCH1/FBXW7 mutation identifies a large subgroup with favorable outcome in adult T-cell acute lymphoblastic leukemia (T-ALL): a Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) study. *Blood*. 2009;113:3918–24.
71. Rousselot P, Huguet F, Rea D, Legros L, Cayuela JM, Maarek O, et al. Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. *Blood*. 2007;109:58–60.
72. Mahon FX, Réa D, Guilhot F, Guilhot F, Huguet F, Nicolini F, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol*. 2010;11:1029–35.
73. Alchalby H, Zabelina T, Stübiger T, van Biezen A, Bornhäuser M, Di Bartolomeo P, et al. Allogeneic stem cell transplantation for myelofibrosis with leukemic transformation. a study of the MPN-subcommittee of the CMWP of the EBMT. *Biol Blood Marrow Transplant*. 2014;20:279–81.
74. Kröger N, Holler E, Kobbe G, Bornhäuser M, Schwerdtfeger R, Baumann H, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Blood*. 2009;114:5264–70.
75. McLornan DP, Sirait T, Hernández-Boluda JC, Czerw T, Hayden P, Yakoub-Agha I. European wide survey on allogeneic haematopoietic cell transplantation practice for myelofibrosis on behalf of the EBMT chronic malignancies working party. *Curr Res Transl Med*. 2021;69:103267.
76. Kröger N, Giorgino T, Scott BL, Ditschkowski M, Alchalby H, Cervantes F, et al. Impact of allogeneic stem cell transplantation on survival of patients less than 65 years of age with primary myelofibrosis. *Blood*. 2015;125:3347–50.
77. Kröger NM, Deeg JH, Olavarria E, Niederwieser D, Bacigalupo A, Barbui T, et al. Indication and management of allogeneic stem cell transplantation in primary myelofibrosis: a consensus process by an EBMT/ELN international working group. *Leukemia*. 2015;29:2126–33.
78. Scott BL, Gooley TA, Sorror ML, Rezvani AR, Linenberger ML, Grim J, et al. The Dynamic International Prognostic Scoring System for myelofibrosis predicts outcomes after hematopoietic cell transplantation. *Blood*. 2012;119:2657–64.
79. Stübiger T, Alchalby H, Ditschkowski M, Wolf D, Wulf G, Zabelina T, et al. JAK inhibition with ruxolitinib as pretreatment for allogeneic stem cell transplantation in primary or post-ET/PV myelofibrosis. *Leukemia*. 2014;28:1736–8.
80. Kröger N, Sbianchi G, Sirait T, Wolschke C, Beelen D, Passweg J, et al. Impact of prior JAK-inhibitor therapy with ruxolitinib on outcome after allogeneic hematopoietic stem cell transplantation for myelofibrosis: a study of the CMWP of EBMT. *Leukemia*. 2021;35:3551–60.
81. Gagelmann N, Ditschkowski M, Bogdanov R, Bredin S, Robin M, Cassinat B, et al. Comprehensive clinical-molecular transplant scoring system for myelofibrosis undergoing stem cell transplantation. *Blood*. 2019;133:2233–42.
82. Gagelmann N, Eikema DJ, Stelljes M, Beelen D, de Wreede L, Mufti G, et al. Optimized EBMT transplant-specific risk score in myelodysplastic syndromes after allogeneic stem-cell transplantation. *Haematologica*. 2019;104:929–36.
83. de Witte T, Bowen D, Robin M, Malcovati L, Niederwieser D, Yakoub-Agha I, et al. Allogeneic hematopoietic stem cell transplantation for MDS and CMML: recommendations from an international expert panel. *Blood*. 2017;129:1753–62.
84. Schanz J, Tuchler H, Sole F, Mallo M, Luno E, Cervera J, et al. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. *J Clin Oncol*. 2012;30:820–9.
85. Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120:2454–65.
86. Della Porta MG, Malcovati L, Boveri E, Travaglio E, Pietra D, Pasutto C, et al. Clinical relevance of bone marrow fibrosis and CD34-positive cell clusters in primary myelodysplastic syndromes. *J Clin Oncol*. 2009;27:754–62.
87. Orazi A, Germing U. The myelodysplastic/myeloproliferative neoplasms: myeloproliferative diseases with dysplastic features. *Leukemia*. 2008;22:1308–19.
88. Itzykson R, Fenaux P, Bowen D, Cross NCP, Cortes J, De Witte T, et al. Diagnosis and treatment of chronic myelomonocytic leukemias in adults: recommendations

- from the European Hematology Association and the European LeukemiaNet. *Hemasphere*. 2018;2:e150.
89. Gagelmann N, Badbaran A, Beelen DW, Salit RB, Stölzel F, Rautenberg C, et al. A prognostic score including mutation profile and clinical features for patients with CMML undergoing stem cell transplantation. *Blood Adv*. 2021;5:1760–9.
  90. Dreger P, Ghia P, Schetelig J, van Gelder M, Kimby E, Michallet M, et al. High-risk chronic lymphocytic leukemia in the era of pathway inhibitors: integrating molecular and cellular therapies. *Blood*. 2018;132:892–902.
  91. Cwynarski K, van Biezen A, de Wreede L, Stilgenbauer S, Bunjes D, Metzner B, et al. Autologous and allogeneic stem-cell transplantation for transformed chronic lymphocytic leukemia (Richter's syndrome): a retrospective analysis from the chronic lymphocytic leukemia subcommittee of the chronic leukemia working party and lymphoma working party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2012;30:2211–7.
  92. Gisselbrecht C, Schmitz N, Mounier N, Singh Gill D, Linch DC, Trneny M, et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. *J Clin Oncol*. 2012;30:4462–9.
  93. Locke FL, Jacobson C, Perales MA, Kersten MJ, Westin JR. Primary analysis of ZUMA-7: a phase 3 randomized trial of axicabtagene ciloleucel (Axi-Cel) versus standard-of-care therapy in patients with relapsed/refractory large B-cell lymphoma. *Blood*. 2021;138:2.
  94. Kamdar MS, Scott R, Arnason, Jon E, Johnston, Patrick B, et al. Lisocabtagene maraleucel (liso-cel), a CD19-directed chimeric antigen receptor (CAR) T cell therapy, versus standard of care (SOC) with salvage chemotherapy (CT) followed by autologous stem cell transplantation (ASCT) as second-line (2L) treatment in patients (Pts) with relapsed or refractory (R/R) large B-cell lymphoma (LBCL): results from the randomized phase 3 transform study. *Blood*. 2021;138:91.
  95. Nastoupil LJ, Jain MD, Feng L, Spiegel JY, Ghobadi A, Lin Y, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. *J Clin Oncol*. 2020;38:3119–28.
  96. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1–2 trial. *Lancet Oncol*. 2019;20:31–42.
  97. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. *N Engl J Med*. 2019;380:45–56.
  98. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. *Lancet*. 2020;396:839–52.
  99. Glass B, Hasenkamp J, Wulf G, Dreger P, Pfreundschuh M, Gramatzki M, et al. Rituximab after lymphoma-directed conditioning and allogeneic stem-cell transplantation for relapsed and refractory aggressive non-Hodgkin lymphoma (DSHNHL R3): an open-label, randomised, phase 2 trial. *Lancet Oncol*. 2014;15:757–66.
  100. van Kampen RJ, Canals C, Schouten HC, Nagler A, Thomson KJ, Vernant JP, et al. Allogeneic stem-cell transplantation as salvage therapy for patients with diffuse large B-cell non-Hodgkin's lymphoma relapsing after an autologous stem-cell transplantation: an analysis of the European Group for Blood and Marrow Transplantation Registry. *J Clin Oncol*. 2011;29:1342–8.
  101. Fenske TS, Ahn KW, Graff TM, DiGilio A, Bashir Q, Kamble RT, et al. Allogeneic transplantation provides durable remission in a subset of DLBCL patients relapsing after autologous transplantation. *Br J Haematol*. 2016;174:235–48.
  102. Thomson KJ, Morris EC, Bloor A, Cook G, Milligan D, Parker A, et al. Favorable long-term survival after reduced-intensity allogeneic transplantation for multiple-relapse aggressive non-Hodgkin's lymphoma. *J Clin Oncol*. 2009;27:426–32.
  103. Doderio A, Patriarca F, Milone G, Sarina B, Miceli R, Iori A, et al. Allogeneic stem cell transplantation for relapsed/refractory B cell lymphomas: results of a multicenter Phase II Prospective Trial including Rituximab in the Reduced-Intensity Conditioning Regimen. *Biol Blood Marrow Transplant*. 2017;23:1102–9.
  104. Herrera AF, Mei M, Low L, Kim HT, Griffin GK, Song JY, et al. Relapsed or refractory double-expressor and double-hit lymphomas have inferior progression-free survival after autologous stem-cell transplantation. *J Clin Oncol*. 2017;35:24–31.
  105. Le Gouill S, Ghesquieres H, Oberic L, Morschhauser F, Tilly H, Ribrag V, et al. Obinutuzumab vs rituximab for advanced DLBCL: a PET-guided and randomized phase 3 study by LYSA. *Blood*. 2021;137:2307–20.
  106. Ferreri AJM, Cwynarski K, Pulczynski E, Fox CP, Schorb E, La Rosee P, et al. Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extracranial Lymphoma Study Group-32 phase 2 trial. *Lancet Haematol*. 2017;4:e510–e23.
  107. Ferreri AJ, Illerhaus G. The role of autologous stem cell transplantation in primary central nervous system lymphoma. *Blood*. 2016;127:1642–9.
  108. Houillier C, Taillandier L, Dureau S, Lamy T, Laadhari M, Chinot O, et al. Radiotherapy or autologous stem-cell transplantation for primary CNS lymphoma in patients 60 years of age and younger: results of the intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study. *J Clin Oncol*. 2019;37:823–33.
  109. Steffanoni S, Calimeri T, Anzalone N, Mastaglio S, Bernardi M, Ferreri AJ. A narrative review of consolidation strategies for young and fit patients with newly-diagnosed primary central nervous system lymphoma. *Expert Rev Hematol*. 2022;15:33–43.
  110. Ferreri AJM, Doorduijn JK, Re A, Cabras MG, Smith J, Ilariucci F, et al. MATRix-RICE therapy and autologous haematopoietic stem-cell transplantation in diffuse large B-cell lymphoma with secondary CNS involvement (MARIETTA): an international, single-arm, phase 2 trial. *Lancet Haematol*. 2021;8:e110–e21.
  111. Sureda A, Bader P, Cesaro S, Dreger P, Duarte RF, Dufour C, et al. Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2015. *Bone Marrow Transplant*. 2015;50:1037–56.
  112. Montoto S, Corradini P, Dreyling M, Ghielmini M, Kimby E, Lopez-Guillermo A, et al. Indications for hematopoietic stem cell transplantation in patients with follicular lymphoma: a consensus project of the EBMT-Lymphoma Working Party. *Haematologica*. 2013;98:1014–21.
  113. Jacobson CA, Chavez JC, Sehgal A, William BM, Munoz J, Salles GA, et al. Outcomes in ZUMA-5 with axicabtagene ciloleucel (axi-cel) in patients (pts) with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) who had the high-risk feature of progression within 24 months from initiation of first anti-CD20-containing chemoimmunotherapy (POD24). *J Clin Oncol*. 2021;39:7515–.
  114. Buske C, Leblond V. How to manage Waldenström's macroglobulinemia. *Leukemia*. 2013;27:762–72.
  115. Kyriakou C, Canals C, Sibon D, Cahn JY, Kazmi M, Arcese W, et al. High-dose therapy and autologous stem-cell transplantation in Waldenström macroglobulinemia: the lymphoma working party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2010;28:2227–32.
  116. Dimopoulos M, Kastrdis E, Owen RG, Kyle RA, Landgren O, Morra E, et al. Treatment recommendations for patients with Waldenström macroglobulinemia (WM) and related disorders: IWWM-7 consensus. *Blood*. 2014;124:1404–11.
  117. Kyriakou C, Canals C, Cornelissen JJ, Socie G, Willemze R, Ibrah N, et al. Allogeneic stem-cell transplantation in patients with Waldenström macroglobulinemia: report from the lymphoma working party of the European group for blood and marrow transplantation. *J Clin Oncol*. 2010;28:4926–34.
  118. Dreyling M, Jurczak W, Jerkeman M, Silva RS, Rusconi C, Trneny M, et al. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study. *Lancet*. 2016;387:770–8.
  119. Martin P, Maddocks K, Leonard JP, Ruan J, Goy A, Wagner-Johnston N, et al. Post-ibrutinib outcomes in patients with mantle cell lymphoma. *Blood*. 2016;127:1559–63.
  120. Dreger P, Michallet M, Bosman P, Dietrich S, Sobh M, Boumendil A, et al. Ibrutinib for bridging to allogeneic hematopoietic cell transplantation in patients with chronic lymphocytic leukemia or mantle cell lymphoma: a study by the EBMT Chronic Malignancies and Lymphoma Working Parties. *Bone Marrow Transplant*. 2019;54:44–52.
  121. Fenske TS, Zhang MJ, Carreras J, Ayala E, Burns LJ, Cashen A, et al. Autologous or reduced-intensity conditioning allogeneic hematopoietic cell transplantation for chemotherapy-sensitive mantle-cell lymphoma: analysis of transplantation timing and modality. *J Clin Oncol*. 2013;32:273–81.
  122. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. *N Engl J Med*. 2020;382:1331–42.
  123. Schmitz N, Nickelsen M, Altmann B, Ziepert M, Bouabdallah K, Gisselbrecht C, et al. Allogeneic or autologous transplantation as first-line therapy for younger patients with peripheral T-cell lymphoma: results of the interim analysis of the AATT trial. *J Clin Oncol*. 2015;33:8507–8507.
  124. Domingo-Domenech E, Duarte RF, Boumendil A, Onida F, Gabriel I, Finel H, et al. Allogeneic hematopoietic stem cell transplantation for advanced mycosis fungoides and Sézary syndrome. An updated experience of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2021;56:1391–401.
  125. Jawed SI, Myskowski PL, Horwitz S, Moskowitz A, Querfeld C. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome): part II. Prognosis, management, and future directions. *J Am Acad Dermatol*. 2014;70:223.e1–17.

126. Trautinger F, Eder J, Assaf C, Bagot M, Cozzio A, Dummer R, et al. European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome—update 2017. *Eur J Cancer*. 2017;77:57–74.
127. Duarte RF, Schmitz N, Servitje O, Sureda A. Haematopoietic stem cell transplantation for patients with primary cutaneous T-cell lymphoma. *Bone Marrow Transplant*. 2008;41:597–604.
128. Duarte RF, Canals C, Onida F, Gabriel IH, Arranz R, Arcese W, et al. Allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and Sézary syndrome: a retrospective analysis of the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2010;28:4492–9.
129. Duarte RF, Boumendil A, Onida F, Gabriel I, Arranz R, Arcese W, et al. Long-term outcome of allogeneic hematopoietic cell transplantation for patients with mycosis fungoides and sézary syndrome: a European society for blood and marrow transplantation lymphoma working party extended analysis. *J Clin Oncol*. 2014;32:3347–8.
130. Linch DC, Winfield D, Goldstone AH, Moir D, Hancock B, McMillan A, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. *Lancet*. 1993;341:1051–4.
131. Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. *Lancet*. 2002;359:2065–71.
132. Sureda A, Canals C, Arranz R, Caballero D, Ribera JM, Brune M, et al. Allogeneic stem cell transplantation after reduced intensity conditioning in patients with relapsed or refractory Hodgkin's lymphoma. Results of the HDR-ALLO study—a prospective clinical trial by the Grupo Espanol de Linfomas/Trasplante de Medula Osea (GEL/TAMO) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *Haematologica*. 2012;97:310–7.
133. Sarina B, Castagna L, Farina L, Patriarca F, Benedetti F, Carella AM, et al. Allogeneic transplantation improves the overall and progression-free survival of Hodgkin lymphoma patients relapsing after autologous transplantation: a retrospective study based on the time of HLA typing and donor availability. *Blood*. 2010;115:3671–7.
134. Messer M, Steinzen A, Vervolgyi E, Lerch C, Richter B, Dreger P, et al. Unrelated and alternative donor allogeneic stem cell transplantation in patients with relapsed or refractory Hodgkin's lymphoma: a systematic review. *Leuk Lymphoma*. 2014;55:296–306.
135. Ramos CA, Grover NS, Beaven AW, Lulla PD, Wu MF, Ivanova A, et al. Anti-CD30 CAR-T cell therapy in relapsed and refractory Hodgkin lymphoma. *J Clin Oncol*. 2020;38:3794–804.
136. Eichenauer DA, Engert A. Current treatment options for nodular lymphocyte-predominant Hodgkin lymphoma. *Curr Opin Oncol*. 2021;33:395–9.
137. Dhakal B, Szabo A, Chhabra S, Hamadani M, D'Souza A, Usmani SZ, et al. Autologous transplantation for newly diagnosed multiple myeloma in the era of novel agent induction: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4:343–50.
138. Wiebach H, Gezer D, Brummendorf TH, Crysandt M, Wilop S. Tolerability of high dose chemotherapy and autologous stem cell transplantation in elderly patients with multiple myeloma: a single-center retrospective analysis. *Curr Res Transl Med*. 2020;68:139–44.
139. Mina R, Petrucci MT, Corradini P, Spada S, Patriarca F, Cerrato C, et al. Treatment intensification with autologous stem cell transplantation and lenalidomide maintenance improves survival outcomes of patients with newly diagnosed multiple myeloma in complete response. *Clin Lymphoma Myeloma Leuk*. 2018;18:533–40.
140. Rodriguez TE, Hari P, Stiff PJ, Smith SE, Sterrenberg D, Vesole DH. Busulfan, melphalan, and bortezomib versus high-dose melphalan as a conditioning regimen for autologous hematopoietic stem cell transplantation in multiple myeloma. *Biol Blood Marrow Transplant*. 2016;22:1391–6.
141. Gagemann N, Eikema DJ, Koster L, Caillot D, Pioltelli P, Lleonart JB, et al. Tandem autologous stem cell transplantation improves outcomes in newly diagnosed multiple myeloma with extramedullary disease and high-risk cytogenetics: a study from the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2019;25:2134–42.
142. Cavo M, Petrucci MT, Di Raimondo F, Zamagni E, Gamberi B, Crippa C, et al. Upfront single versus double autologous stem cell transplantation for newly diagnosed multiple myeloma: an intergroup, multicenter, Phase III Study of the European Myeloma Network (EMN02/HO95 MM Trial). *Blood*. 2016;128:991.
143. Cavo M, Beksac M, Dimopoulos MA, Pantani L, Gay F, Hájek R, et al. Intensification therapy with bortezomib-melphalan-prednisone versus autologous stem cell transplantation for newly diagnosed multiple myeloma: an intergroup, multicenter, Phase III Study of the European Myeloma Network (EMN02/HO95 MM Trial). *Blood*. 2016;128:673.
144. Attal M, Lauwers-Cances V, Marit G, Caillot D, Moreau P, Facon T, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1782–91.
145. McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med*. 2012;366:1770–81.
146. Jimenez-Zepeda VH, Mikhael J, Winter A, Franke N, Masih-Khan E, Trudel S, et al. Second autologous stem cell transplantation as salvage therapy for multiple myeloma: impact on progression-free and overall survival. *Biol Blood Marrow Transplant*. 2012;18:773–9.
147. Beksac M, Savani BN. Prognostic scoring system after transplantation in myeloma: predicting early relapse. *Br J Haematol*. 2020;191:323–4.
148. Sobh M, Michallet M, Gahrton G, Iacobelli S, van Biezen A, Schönland S, et al. Allogeneic hematopoietic cell transplantation for multiple myeloma in Europe: trends and outcomes over 25 years. A study by the EBMT Chronic Malignancies Working Party. *Leukemia*. 2016;30:2047–54.
149. Bruno B, Rotta M, Patriarca F, Mordini N, Allione B, Carnevale-Schianca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. *N Engl J Med*. 2007;356:1110–20.
150. Gahrton G, Iacobelli S, Björkstrand B, Hegenbart U, Gruber A, Greinix H, et al. Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study. *Blood*. 2013;121:5055–63.
151. Rosinol L, Perez-Simon JA, Sureda A, de la Rubia J, de Arriba F, Lahuerta JJ, et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. *Blood*. 2008;112:3591–3.
152. Patriarca F, Einsele H, Spina F, Bruno B, Isola M, Nozzoli C, et al. Allogeneic stem cell transplantation in multiple myeloma relapsed after autograft: a multicenter retrospective study based on donor availability. *Biol Blood Marrow Transplant*. 2012;18:617–26.
153. Ghosh N, Ye X, Tsai HL, Bolaños-Meade J, Fuchs EJ, Luznik L, et al. Allogeneic blood or marrow transplantation with post-transplantation cyclophosphamide as graft-versus-host disease prophylaxis in multiple myeloma. *Biol Blood Marrow Transplant*. 2017;23:1903–9.
154. Beksac M, Kröger N, Byrne JL, Ganser A, Yegin AZ, Schönland S. Allogeneic hematopoietic cell transplantation (allo-HCT) outcomes in myeloma patients on renal replacement therapy: a report from the Chronic Malignancy Working Party (CMWP) of the European Society of Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant*. 2021;56:529–31.
155. Beauvais D, Danhof S, Hayden PJ, Einsele H, Yakoub-Agha I. Clinical data, limitations and perspectives on chimeric antigen receptor T-cell therapy in multiple myeloma. *Curr Opin Oncol*. 2020;32:418–26.
156. Munshi NC, Anderson LD Jr, Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. *N Engl J Med*. 2021;384:705–16.
157. Berdeja JG, Madduri D, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. *Lancet*. 2021;398:314–24.
158. Dispenzieri A, Kyle RA, Lacy MQ, Therneau TM, Larson DR, Plevak MF, et al. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study. *Blood*. 2004;103:3960–3.
159. Jaccard A, Moreau P, Leblond V, Leleu X, Benboubker L, Hermine O, et al. High-dose melphalan versus melphalan plus dexamethasone for AL amyloidosis. *N Engl J Med*. 2007;357:1083–93.
160. D'Souza A, Dispenzieri A, Wirk B, Zhang MJ, Huang J, Gertz MA, et al. Improved outcomes after autologous hematopoietic cell transplantation for light chain amyloidosis: a Center for International Blood and Marrow Transplant Research Study. *J Clin Oncol*. 2015;33:3741–9.
161. Sidiqi MH, Aljama MA, Buadi FK, Warsame RM, Lacy MQ, Dispenzieri A, et al. Stem cell transplantation for light chain amyloidosis: decreased early mortality over time. *J Clin Oncol*. 2018;36:1323–9.
162. Bochtler T, Hegenbart U, Kunz C, Benner A, Kimmich C, Seckinger A, et al. Prognostic impact of cytogenetic aberrations in AL amyloidosis patients after high-dose melphalan: a long-term follow-up study. *Blood*. 2016;128:594–602.
163. Schönland SO, Dreger P, de Witte T, Hegenbart U. Current status of hematopoietic cell transplantation in the treatment of systemic amyloid light-chain amyloidosis. *Bone Marrow Transplant*. 2012;47:895–905.
164. Marsh JC, Ball SE, Cavenagh J, Derbyshire P, Dokal I, Gordon-Smith EC, et al. Guidelines for the diagnosis and management of aplastic anaemia. *Br J Haematol*. 2009;147:43–70.

165. Scheinberg P, Young NS. How I treat acquired aplastic anemia. *Blood*. 2012;120:1185–96.
166. Giammarco S, Peffault de Latour R, Sica S, Dufour C, Socie G, Passweg J, et al. Transplant outcome for patients with acquired aplastic anemia over the age of 40: has the outcome improved? *Blood*. 2018;131:1989–92.
167. Bacigalupo A, Socié G, Schrezenmeier H, Tichelli A, Locasciulli A, Fuehrer M, et al. Bone marrow versus peripheral blood matched sibling transplants, in acquired aplastic anemia: survival advantage for marrow in all age groups. *Haematologica*. 2012;97:1142–8.
168. Marsh JC, Gupta V, Lim Z, Ho AY, Ireland RM, Hayden J, et al. Alemtuzumab with fludarabine and cyclophosphamide reduces chronic graft-versus-host disease after allogeneic stem cell transplantation for acquired aplastic anaemia. *Blood*. 2011;118:2351–7.
169. Marsh JC, Pearce RM, Koh MB, Lim Z, Pagliuca A, Mufti GJ, et al. Retrospective study of Alemtuzumab versus ATG based conditioning without irradiation for unrelated and matched sibling donor transplants in acquired severe aplastic anaemia: a study from the British Society for Blood and Marrow Transplantation (BSBMT). *Bone Marrow Transplant*. 2014;49:42–48.
170. Bacigalupo A, Marsh JC. Unrelated donor search and unrelated donor transplantation in the adult aplastic anaemia patient aged 18–40 years without an HLA-identical sibling and failing immunosuppression. *Bone Marrow Transplant*. 2013;48:198–200.
171. de Latour RP. Transplantation for bone marrow failure: current issues. *Hematology Am Soc Hematol Educ Program*. 2016;2016:90–8.
172. Olnes MJ, Scheinberg P, Calvo KR, Desmond R, Tang Y, Dumitriu B, et al. Eltrombopag and improved hematopoiesis in refractory aplastic anemia. *N Engl J Med*. 2012;367:11–19.
173. Desmond R, Townsley DM, Dumitriu B, Olnes MJ, Scheinberg P, Bevans M, et al. Eltrombopag restores trilineage hematopoiesis in refractory severe aplastic anemia that can be sustained on discontinuation of drug. *Blood*. 2014;123:1818–25.
174. Lengline E, Drenou B, Peterlin P, Tournilhac O, Abraham J, Berceanu A, et al. Nationwide survey on the use of eltrombopag in patients with severe aplastic anemia: a report on behalf of the French Reference Center for Aplastic Anemia. *Haematologica*. 2018;103:212–20.
175. DeZern AE, Zahurak M, Symons H, Cooke K, Jones RJ, Brodsky RA. Alternative donor transplantation with high-dose post-transplantation cyclophosphamide for refractory severe aplastic anemia. *Biol Blood Marrow Transplant*. 2017;23:498–504.
176. Peffault de Latour R, Purtil D, Ruggeri A, Sanz G, Michel G, Gandemer V, et al. Influence of nucleated cell dose on overall survival of unrelated cord blood transplantation for patients with severe acquired aplastic anaemia. A study by Eurocord and the Aplastic Anaemia Working Party of the European Group for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2010;1:78–85.
177. De Latour RP, Rocha V, Socie G. Cord blood transplantation in aplastic anaemia. *Bone Marrow Transplant*. 2013;48:201–2.
178. Ciceri F, Lupo-Stanghellini MT, Korthof ET. Haploidentical transplantation in patients with acquired aplastic anaemia. *Bone Marrow Transplant*. 2013;48:183–5.
179. Clay J, Kulasekarara AG, Potter V, Grimaldi F, McLornan D, Raj K, et al. Non-myeloablative peripheral blood haploidentical stem cell transplantation for refractory severe aplastic anemia. *Biol Blood Marrow Transplant*. 2014;20:1711–6.
180. Pagliuca S, Peffault de Latour R, Volt F, Locatelli F, Zecca M, Dalle JH, et al. Long-term outcomes of cord blood transplantation from an HLA-identical sibling for patients with bone marrow failure syndromes: a report from Eurocord, Cord Blood Committee and Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2017;23:1939–48.
181. Bacigalupo A. Alternative donor transplants for severe aplastic anemia. *Hematol Am Soc Hematol Educ Program*. 2018;2018:467–73.
182. DeZern AE, Zahurak ML, Symons HJ, Cooke KR, Rosner GL, Gladstone DE, et al. Haploidentical BMT for severe aplastic anemia with intensive GVHD prophylaxis including posttransplant cyclophosphamide. *Blood Adv*. 2020;4:1770–9.
183. Prata PH, Eikema DJ, Afansyev B, Bosman P, Smiers F, Diez-Martin JL, et al. Haploidentical transplantation and posttransplant cyclophosphamide for treating aplastic anemia patients: a report from the EBMT Severe Aplastic Anemia Working Party. *Bone Marrow Transplant*. 2020;55:1050–8.
184. de Latour PR, Schrezenmeier H, Bacigalupo A, Blaise D, de Souza CA, Vigouroux S, et al. Allogeneic stem cell transplantation in paroxysmal nocturnal hemoglobinuria. *Haematologica*. 2012;97:1666–73.
185. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. *Blood*. 2014;124:2804–11.
186. Barkholt L, Bregni M, Remberger M, Blaise D, Peccatori J, Massenkeil G, et al. Allogeneic haematopoietic stem cell transplantation for metastatic renal carcinoma in Europe. *Ann Oncol*. 2006;17:1134–40.
187. Carnevale-Schianca F, Cignetti A, Capaldi A, Vitaggio K, Vallario A, Ricchiardi A, et al. Allogeneic nonmyeloablative hematopoietic cell transplantation in metastatic colon cancer: tumor-specific T cells directed to a tumor-associated antigen are generated in vivo during GVHD. *Blood*. 2006;107:3795–803.
188. Secondino S, Zecca M, Licitra L, Gurrado A, Schiavetto I, Bossi P, et al. T-cell therapy for EBV-associated nasopharyngeal carcinoma: preparative lymphodepleting chemotherapy does not improve clinical results. *Ann Oncol*. 2012;23:435–41.
189. Mehta GU, Malekzadeh P, Shelton T, White DE, Butman JA, Yang JC, et al. Outcomes of adoptive cell transfer with tumor-infiltrating lymphocytes for metastatic melanoma patients with and without brain metastases. *J Immunother*. 2018;41:241–7.
190. Bregni M, Badoglio M, Pedrazzoli P, Lanza F. Is allogeneic transplant for solid tumors still alive? *Bone Marrow Transplant*. 2016;51:751–2.
191. Comoli P, Chabannon C, Koehl U, Lanza F, Urbano-Ispizua A, Hudecek M, et al. Development of adaptive immune effector therapies in solid tumors. *Ann Oncol*. 2019;30:1740–50.
192. Berry DA, Ueno NT, Johnson MM, Lei X, Caputo J, Rodenhuis S, et al. High dose chemotherapy with autologous stem cell support versus standard-dose chemotherapy: overview of individual patient data from 15 randomized adjuvant therapy breast cancer trials. *J Clin Oncol*. 2011;29:3214–23.
193. Berry DA, Ueno NT, Johnson MM, Lei X, Caputo J, Smith DA, et al. High-dose chemotherapy with autologous hematopoietic stem-cell transplantation in metastatic breast cancer: overview of six randomized trials. *J Clin Oncol*. 2011;29:3224–31.
194. Martino M, Bottini A, Rosti G, Generali D, Secondino S, Barni S, et al. Critical issues on high-dose chemotherapy with autologous hematopoietic progenitor cell transplantation in breast cancer patients. *Expert Opin Biol Ther*. 2012;12:1505–15.
195. Steenbruggen TG, Steggink LC, Seynaeve CM, van der Hoeven JJM, Hoening MJ, Jager A, et al. High-dose chemotherapy with hematopoietic stem cell transplant in patients with high-risk breast cancer and 4 or more involved axillary lymph nodes—20-year follow-up of a phase 3 randomized clinical trial. *JAMA Oncol*. 2020;6:528–34. <https://doi.org/10.1001/jamaoncol.2019.6276>.
196. Martino M, Lanza F, Pavesi L, Öztürk M, Blaise D, Leno Núñez R, et al. High-dose chemotherapy and autologous hematopoietic stem cell transplantation as adjuvant treatment in high-risk breast cancer: data from the European Group for Blood and Marrow Transplantation Registry. *Biol Blood Marrow Transplant*. 2016;22:475–81.
197. Martino M, Ballestrero A, Zambelli A, Secondino S, Aieta M, Bengala C, et al. Long-term survival in patients with metastatic breast cancer receiving intensified chemotherapy and stem cell rescue: data from the Italian registry. *Bone Marrow Transplant*. 2013;48:414–8.
198. Schouten PC, Gluz O, Harbeck N, Mohrmann S, Diallo-Danebrock R, Pelz E, et al. BRCA1-like profile predicts benefit of tandem high dose epirubicin-cyclophosphamide-thiotepa in high risk breast cancer patients randomized in the WSG-AM01 trial. *Int J Cancer*. 2016;139:882–9.
199. Boudin L, Chabannon C, Sfumato P, Sabatier R, Bertucci F, Tarpin C, et al. Immunohistochemical subtypes predict survival in metastatic breast cancer receiving high-dose chemotherapy with autologous haematopoietic stem cell transplantation. *Eur J Cancer*. 2016;57:118–26.
200. Necchi A, Lanza F, Rosti G, Martino M, Farè E, Pedrazzoli P. European Society for Blood and Marrow Transplantation, Solid Tumors Working Party (EBMT-STWP) and the Italian Germ Cell Cancer Group (IGG) High-dose chemotherapy for germ cell tumors: do we have a model?. *Expert Opin Biol Ther*. 2015;15:33–44.
201. Agrawal V, Abonour R, Abu Zaid M, Althouse SK, Ashkar R, Albany C, et al. Survival outcomes and toxicity in patients 40 years old or older with relapsed metastatic germ cell tumors treated with high-dose chemotherapy and peripheral blood stem cell transplantation. *Cancer*. 2021;127:3751–60. <https://doi.org/10.1002/cncr.33771>.
202. Lorch A, Bascoul-Mollevi C, Kramar A, Einhorn L, Necchi A, Massard C, et al. Conventional-dose versus high-dose chemotherapy as first salvage treatment in male patients with metastatic germ cell tumors: evidence from a large international database. *J Clin Oncol*. 2011;29:2178–84.
203. Ladenstein R, Pötschger U, Le Deley MC, Whelan J, Paulussen M, Oberlin O, et al. Primary disseminated multifocal EWING sarcoma: results of the Euro-EWING 99 trial. *J Clin Oncol*. 2010;28:3284–91.
204. Heilig CE, Badoglio M, Labopin M, Fröhling S, Secondino S, Heinz J, et al. Haematopoietic stem cell transplantation in adult soft-tissue sarcoma: an analysis from the European Society for Blood and Marrow Transplantation. *ESMO Open*. 2020;5:e000860.
205. Spreafico F, Massimino M, Gandola L, Cefalo G, Mazza E, Landonio G, et al. Survival of adults treated for medulloblastoma using paediatric protocols. *Eur J Cancer*. 2005;41:1304–10.

206. Alexander T, Greco R, Snowden JA. Hematopoietic stem cell transplantation for autoimmune disease. *Annu Rev Med.* 2021;72:215–28.
207. Passweg JR, Baldomero H, Chabannon C, Basak GW, de la Cámara R, Corbacioglu S, et al. Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 years. *Bone Marrow Transplant* 2021;56:1651–64.
208. Boffa G, Massacesi L, Inglesse M, Mariottini A, Capobianco M, Lucia M, et al. Long-term clinical outcomes of hematopoietic stem cell transplantation in multiple sclerosis. *Neurology.* 2021. <https://doi.org/10.1212/WNL.00000000000011461> Online ahead of print.
209. Burt RK, Balabanov R, Burman J, Sharrack B, Snowden JA, Oliveira MC, et al. Effect of nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis: a randomized clinical trial. *JAMA.* 2019;321:165–74.
210. Muraro PA, Pasquini M, Atkins HL, Bowen JD, Farge D, Fassas A, et al. Long-term outcomes after autologous hematopoietic stem cell transplantation for multiple sclerosis. *JAMA Neurol.* 2017;74:459–69.
211. Das J, Snowden JA, Burman J, Freedman MS, Atkins H, Bowman M, et al. Autologous haematopoietic stem cell transplantation as a first-line disease-modifying therapy in patients with 'aggressive' multiple sclerosis. *Mult Scler.* 2021;27:1198–204.
212. Tappenden P, Wang Y, Sharrack B, Burman J, Kazmi M, Saccardi R, et al. Evaluating the clinical effectiveness of autologous haematopoietic stem cell transplantation versus disease-modifying therapy in multiple sclerosis using a matching-adjusted indirect comparison: an exploratory study from the Autoimmune Diseases Working Party (ADWP) of the European Society of Bone and Marrow Transplantation (EBMT). *Bone Marrow Transplant.* 2020;55:1473–5.
213. Burt RK, Shah SJ, Dill K, Grant T, Gheorghiadu M, Schroeder J, et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. *Lancet.* 2011;378:498–506.
214. van Laar JM, Farge D, Sont JK, Naraghi K, Marjanovic Z, Larghero J, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. *JAMA.* 2014;311:2490–8.
215. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, McSweeney PA, Pinckney A, Welch B, et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. *N Engl J Med.* 2018;378:35–47.
216. Henes J, Oliveira MC, Labopin M, Badoglio M, Scherer HU, del Papa N, et al. Autologous stem cell transplantation for progressive systemic sclerosis: a prospective non-interventional study from the European Society for Blood and Marrow Transplantation Autoimmune Disease Working Party. *Haematologica.* 2021;106:375–83.
217. Burt RK, Han X, Quigley K, Arnautovic I, Shah SJ, Lee DC, et al. Cardiac safe hematopoietic stem cell transplantation for systemic sclerosis with poor cardiac function: a pilot safety study that decreases neutropenic interval to 5 days. *Bone Marrow Transplant.* 2021;56:50–59.
218. Hawkey CJ, Allez M, Clark MM, Labopin M, Lindsay JO, Ricart E, et al. Autologous hematopoietic stem cell transplantation for refractory Crohn disease: a randomized clinical trial. *JAMA.* 2015;314:2524–34.
219. Lindsay JO, Allez M, Clark M, Labopin M, Ricart E, Rogler G, et al. Autologous stem-cell transplantation in treatment-refractory Crohn's disease: an analysis of pooled data from the ASTIC trial. *Lancet Gastroenterol Hepatol.* 2017;2:399–406.
220. Burt RK, Han X, Gozdzik P, Young K, Morgan A, Clendenan AM, et al. Five year follow-up after autologous peripheral blood hematopoietic stem cell transplantation for refractory, chronic, corticosteroid-dependent systemic lupus erythematosus: effect of conditioning regimen on outcome. *Bone Marrow Transplant.* 2018;53:692–700.
221. Alexander T, Thiel A, Rosen O, Massenkeil G, Sattler A, Kohler S, et al. Depletion of autoreactive immunologic memory followed by autologous hematopoietic stem cell transplantation in patients with refractory SLE induces long-term remission through de novo generation of a juvenile and tolerant immune system. *Blood.* 2009;113:214–23.
222. Greco R, Bondanza A, Oliveira MC, Badoglio M, Burman J, Piehl F, et al. Autologous hematopoietic stem cell transplantation in neuromyelitis optica: a registry study of the EBMT Autoimmune Diseases Working Party. *Mult Scler.* 2015;21:189–97.
223. Burt RK, Balabanov R, Han X, Burns C, Gastala J, Jovanovic B, et al. Autologous nonmyeloablative hematopoietic stem cell transplantation for neuromyelitis optica. *Neurology.* 2019;93:e1732–e1741.
224. Burt RK, Balabanov R, Tavee J, Han X, Sufit R, Ajroud-Driss S, et al. Hematopoietic stem cell transplantation for chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol.* 2020;267:3378–91.
225. Bryant A, Atkins H, Pringle CE, Allan D, Anstee G, Bence-Bruckler I, et al. Myasthenia gravis treated with autologous hematopoietic stem cell transplantation. *JAMA Neurol.* 2016;73:652–8.
226. Kass-Iliyya L, Snowden JA, Thorpe A, Jessop H, Chantry AD, Sarrigiannis PG, et al. Autologous haematopoietic stem cell transplantation for refractory stiff-person syndrome: the UK experience. *J Neurol.* 2021;268:265–75.
227. Burt RK, Balabanov R, Han X, Quigley K, Arnautovic I, Helenowski I, et al. Autologous hematopoietic stem cell transplantation for stiff-person spectrum disorder: a clinical trial. *Neurology.* 2021;96:e817–e830.
228. Alexander T, Samuelson C, Daikeler T, Henes J, Akil M, Skagerlind L, et al. Autologous haematopoietic stem cell transplantation (HSCT) for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis: a retrospective survey of patients reported to European Society for Blood and Marrow Transplantation (EBMT) registry. *Bone Marrow Transplant.* 2020;55:1512–5.
229. Laurent C, Marjanovic Z, Ricard L, Henes J, Dulery R, Badoglio M, et al. Autologous hematopoietic stem cell transplantation with reduced-intensity conditioning regimens in refractory Takayasu arteritis: a retrospective multicenter case-series from the Autoimmune Diseases Working Party (ADWP) of the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant.* 2020;55:2109–13.
230. Puyade M, Patel A, Lim YJ, Blank N, Badoglio M, Gualandi F, et al. Autologous hematopoietic stem cell transplantation for behcet's disease: a retrospective survey of patients treated in europe, on behalf of the Autoimmune Diseases Working Party of the European Society for Blood and Marrow Transplantation. *Front Immunol.* 2021;12:638709.
231. Nijeboer P, van Wanrooij R, van Gils T, Wierdsma NJ, Tack GJ, Bitte BI, et al. Lymphoma development and survival in refractory coeliac disease type II: Histological response as prognostic factor. *United European. Gastroenterol J.* 2017;5:208–17.
232. Snowden JA, Badoglio M, Labopin M, Biebel S, McGrath E, Marjanovic Z, et al. Evolution, trends, outcomes, and economics of hematopoietic stem cell transplantation in severe autoimmune diseases. *Blood Adv.* 2017;1:2742–55.
233. Burt RK, Tappenden P, Han X, Quigley K, Arnautovic I, Sharrack B, et al. Health economics and patient outcomes of hematopoietic stem cell transplantation versus disease-modifying therapies for relapsing remitting multiple sclerosis in the United States of America. *Mult Scler Relat Disord.* 2020;45:102404.
234. Burt RK, Tappenden P, Balabanov R, Han X, Quigley K, Snowden JA, et al. The cost effectiveness of immunoglobulin vs. hematopoietic stem cell transplantation for CIDP. *Front Neurol.* 2021;12:645263.
235. Greco R, Labopin M, Badoglio M, Veys P, Furtado Silva JM, Abinun M, et al. Allogeneic HSCT for autoimmune diseases: a retrospective study from the EBMT ADWP, IEWP, and PDWP Working Parties. *Front Immunol.* 2019;10:1570.
236. Greco R, Alexander T, Burman J, Del Papa N, de Vries-Bouwstra J, Farge D, et al. Hematopoietic stem cell transplantation for autoimmune diseases in the time of COVID-19: EBMT guidelines and recommendations. *Bone Marrow Transplant.* 2021;56:1493–508.
237. Sharrack B, Saccardi R, Alexander T, Badoglio M, Burman J, Farge D, et al. Autologous haematopoietic stem cell transplantation and other cellular therapy in multiple sclerosis and immune-mediated neurological diseases: updated guidelines and recommendations from the EBMT Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of EBMT and ISCT (JACIE). *Bone Marrow Transplant.* 2020;55:283–306.
238. Farge D, Burt RK, Oliveira MC, Mousseaux E, Rovira M, Marjanovic Z, et al. Cardiopulmonary assessment of patients with systemic sclerosis for hematopoietic stem cell transplantation: recommendations from the European Society for Blood and Marrow Transplantation Autoimmune Diseases Working Party and collaborating partners. *Bone Marrow Transplant.* 2017;52:1495–503.
239. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis.* 2017;76:1327–39.
240. Snowden JA, Panés J, Alexander T, Allez M, Ardizzone S, Dierckx D, et al. Autologous haematopoietic stem cell transplantation (AHSCT) in severe Crohn's disease: a review on behalf of ECCO and EBMT. *J Crohns Colitis.* 2018;12:476–88.
241. Jessop H, Farge D, Saccardi R, Alexander T, Rovira M, Sharrack B, et al. General information for patients and carers considering haematopoietic stem cell transplantation (HSCT) for severe autoimmune diseases (ADS): a position statement from the EBMT Autoimmune Diseases Working Party (ADWP), the EBMT Nurses Group, the EBMT Patient, Family and Donor Committee and the Joint Accreditation Committee of ISCT and EBMT (JACIE). *Bone Marrow Transplant.* 2019;54:933–42.
242. Roberts F, Hobbs H, Jessop H, Bozzolini C, Burman J, Greco R, et al. Rehabilitation before and after autologous haematopoietic stem cell transplantation (AHSCT) for patients with multiple sclerosis (MS): consensus guidelines and recommendations for best clinical practice on behalf of the Autoimmune Diseases Working Party, Nurses Group, and Patient Advocacy Committee of the European

- Society for Blood and Marrow Transplantation (EBMT). *Front Neurol*. 2020;11:556141.
243. Ismail A, Sharrack B, Saccardi R, Moore JJ, Snowden JA. Autologous haematopoietic stem cell therapy for multiple sclerosis: a review for supportive care clinicians on behalf of the Autoimmune Diseases Working Party of the European Society for Blood and Marrow Transplantation. *Curr Opin Support Palliat Care*. 2019;13:394–401.
  244. Burns SO, Morris EC. How I use allogeneic HSCT for adults with inborn errors of immunity. *Blood*. 2021;138:1666–76.
  245. Niewerth D, Creutzig U, Bierings MB, Kaspers GJ. A review on allogeneic stem cell transplantation for newly diagnosed pediatric acute myeloid leukemia. *Blood*. 2010;116:2205–14.
  246. Burke MJ, Wagner JE, Cao Q, Ustun C, Verneris MR. Allogeneic hematopoietic cell transplantation in first remission abrogates poor outcomes associated with high-risk pediatric acute myeloid leukemia. *Biol Blood Marrow Transplant*. 2013;19:1021–5.
  247. Klusmann JH, Reinhardt D, Zimmermann M, Kremens B, Vormoor J, Dworzak M, et al. The role of matched sibling donor allogeneic stem cell transplantation in pediatric high-risk acute myeloid leukemia: results from the AML-BFM 98 study. *Haematologica*. 2012;97:21–29.
  248. Creutzig U, Zimmermann M, Bourquin JP, Dworzak MN, Kremens B, Lehrnbecher T, et al. Favorable outcome in infants with AML after intensive first- and second-line treatment: an AML-BFM study group report. *Leukemia*. 2012;26:654–61.
  249. Marks D, Khattry N, Cummins M, Goulden N, Green A, Harvey J, et al. Haploidentical stem cell transplantation for children with acute leukaemia. *Br J Haematol*. 2006;134:196–201.
  250. Locatelli F, Pende D, Maccario R, Mingari MC, Moretta A, Moretta L. Haploidentical hemopoietic stem cell transplantation for the treatment of high-risk leukemias: how NK cells make the difference. *Clin Immunol*. 2009;133:171–8.
  251. Hasle H. A critical review of which children with acute myeloid leukaemia need stem cell procedures. *Br J Haematol*. 2014;166:23–33.
  252. Mann G, Attarbaschi A, Schrappe M, De Lorenzo P, Peters C, Hann I, et al. Improved outcome with hematopoietic stem cell transplantation in a poor prognostic subgroup of infants with mixed-lineage-leukemia (MLL)-rearranged acute lymphoblastic leukemia: results from the Interfant-99 Study. *Blood*. 2010;116:2644–50.
  253. von Stackelberg A, Volzke E, Kuhl JS, Seeger K, Schrauder A, Escherich G, et al. Outcome of children and adolescents with relapsed acute lymphoblastic leukaemia and non-response to salvage protocol therapy: a retrospective analysis of the ALL-REZ BFM Study Group. *Eur J Cancer*. 2011;47:90–97.
  254. Peters C, Cornish JM, Parikh SH, Kurtzberg J. Stem cell source and outcome after hematopoietic stem cell transplantation (HSCT) in children and adolescents with acute leukemia. *Pedia Clin North Am*. 2010;57:27–46.
  255. Schrauder A, von Stackelberg A, Schrappe M, Cornish J, Peters C. Allogeneic hematopoietic SCT in children with ALL: current concepts of ongoing prospective SCT trials. *Bone Marrow Transplant*. 2008;41:571–74.
  256. Peters C, Schrappe M, von Stackelberg A, Schrauder A, Bader P, Ebell W, et al. Stem-cell transplantation in children with acute lymphoblastic leukemia: A prospective international multicenter trial comparing sibling donors with matched unrelated donors-The ALL-SCT-BFM-2003 trial. *J Clin Oncol*. 2015;33:1265–74.
  257. Pulsipher MA, Peters C, Pui CH. High-risk pediatric acute lymphoblastic leukemia: to transplant or not to transplant? *Biol Blood Marrow Transplant*. 2011;17:137–148.
  258. Bader P, Kreyenberg H, Henze GH, Eckert C, Reising M, Willasch A, et al. Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group. *J Clin Oncol*. 2009;27:377–84.
  259. Eckert C, Henze G, Seeger K, Hagedorn N, Mann G, Panzer-Grumayer R, et al. Use of allogeneic hematopoietic stem-cell transplantation based on minimal residual disease response improves outcomes for children with relapsed acute lymphoblastic leukemia in the intermediate-risk group. *J Clin Oncol*. 2013;31:2736–42.
  260. Bader P, Kreyenberg H, von Stackelberg A, Eckert C, Salzmann-Manrique E, Meisel R, et al. Monitoring of minimal residual disease after allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia allows for the identification of impending relapse: results of the ALL-BFM-SCT 2003 trial. *J Clin Oncol*. 2015;33:1275–84.
  261. Beck JC, Cao Q, Trotz B, Smith AR, Weigel BJ, Verneris MR, et al. Allogeneic hematopoietic cell transplantation outcomes for children with B-precursor acute lymphoblastic leukemia and early or late BM relapse. *Bone Marrow Transplant*. 2011;46:950–5.
  262. Meisel R, Klingebiel T, Dilloo D. German/Austrian Pediatric Registry for Stem Cell Transplantation Peripheral blood stem cells versus bone marrow in pediatric unrelated donor stem cell transplantation. *Blood*. 2013;121:863–5.
  263. Peters C, Dalle JH, Locatelli F, Poetschger U, Sedlacek P, Buechner J, et al. Total body irradiation or chemotherapy conditioning in childhood ALL: a multinational, randomized, noninferiority Phase III study. *J Clin Oncol*. 2021;39:295–307.
  264. Suttorp M, Eckardt L, Tauer JT, Millot F. Management of chronic myeloid leukemia in childhood. *Curr Hematologic Malignancy Rep*. 2012;7:116–24.
  265. Suttorp M, Yaniv I, Schultz KR. Controversies in the treatment of CML in children and adolescents: TKIs versus BMT? *Biol Blood Marrow Transplant*. 2011;17: S115–122.
  266. de la Fuente J, Baruchel A, Biondi A, de Bont E, Dresse MF, Suttorp M, et al. Managing children with chronic myeloid leukaemia (CML): recommendations for the management of CML in children and young people up to the age of 18 years. *Br J Haematol*. 2014;167:33–47.
  267. Jaeger BA, Tauer JT, Ulmer A, Kuhlisch E, Roth HJ, Suttorp M. Changes in bone metabolic parameters in children with chronic myeloid leukemia on imatinib treatment. *Med Sci Monit*. 2012;18:721–8.
  268. Ulmer A, Tabea Tauer J, Glauche I, Jung R, Suttorp M. TK inhibitor treatment disrupts growth hormone axis: clinical observations in children with CML and experimental data from a juvenile animal model. *Klinische Padiatrie*. 2013;225:120–6.
  269. Suttorp M, Claviez A, Bader P, Peters C, Gadner H, Ebell W, et al. Allogeneic stem cell transplantation for pediatric and adolescent patients with CML: results from the prospective trial CML-paed I. *Klinische Padiatrie*. 2009;221:351–7.
  270. Millot F, Claviez A, Leverger G, Corbaciglu S, Groll AH, Suttorp M. Imatinib cessation in children and adolescents with chronic myeloid leukemia in chronic phase. *Pediatr Blood Cancer*. 2014;61:355–7.
  271. Locatelli F, Crotta A, Ruggeri A, Eapen M, Wagner JE, Macmillan ML, et al. Analysis of risk factors influencing outcomes after cord blood transplantation in children with juvenile myelomonocytic leukemia: a EUROCORD, EBMT, EWOG-MDS, CIBMTR study. *Blood*. 2013;122:2135–41.
  272. Madureira AB, Eapen M, Locatelli F, Teira P, Zhang MJ, Davies SM, et al. Analysis of risk factors influencing outcome in children with myelodysplastic syndrome after unrelated cord blood transplantation. *Leukemia*. 2011;25:449–54.
  273. Strahm B, Nollke P, Zecca M, Korthof ET, Bierings M, Furlan I, et al. Hematopoietic stem cell transplantation for advanced myelodysplastic syndrome in children: results of the EWOG-MDS 98 study. *Leukemia*. 2011;25:455–62.
  274. Burkhardt B, Reiter A, Landmann E, Lang P, Lassay L, Dickerhoff R, et al. Poor outcome for children and adolescents with progressive disease or relapse of lymphoblastic lymphoma: a report from the berlin-frankfurt-muenster group. *J Clin Oncol*. 2009;27:3363–9.
  275. Gross TG, Hale GA, He W, Camitta BM, Sanders JE, Cairo MS, et al. Hematopoietic stem cell transplantation for refractory or recurrent non-Hodgkin lymphoma in children and adolescents. *Biol Blood Marrow Transplant*. 2010;16:223–30.
  276. Woessmann W, Peters C, Lenhard M, Burkhardt B, Sykora KW, Dilloo D, et al. Allogeneic haematopoietic stem cell transplantation in relapsed or refractory anaplastic large cell lymphoma of children and adolescents—a Berlin-Frankfurt-Munster group report. *Br J Haematol*. 2006;133:176–82.
  277. Kelly KM. Hodgkin lymphoma in children and adolescents: improving the therapeutic index. *Blood*. 2015;126:2452–8.
  278. Kahn JM, Kelly KM. Adolescent and young adult Hodgkin lymphoma: raising the bar through collaborative science and multidisciplinary care. *Pediatr Blood Cancer*. 2018;65:e27033.
  279. Ladenstein R, Pötschger U, Hartman O, Pearson AD, Klingebiel T, Castel V, et al. 28 years of high-dose therapy and SCT for neuroblastoma in Europe: lessons from more than 4000 procedures. *Bone Marrow Transplant*. 2008;41:S118–127.
  280. Matthay KK, Reynolds CP, Seeger RC, Shimada H, Adkins ES, Haas-Kogan D, et al. Long-term results for children with high-risk neuroblastoma treated on a randomized trial of myeloablative therapy followed by 13-cis-retinoic acid: a children's oncology group study. *J Clin Oncol*. 2009;27:1007–13.
  281. Samarasinghe A, Webb DK. How I manage aplastic anaemia in children. *Br J Haematol*. 2012;157:26–40.
  282. Samarasinghe S, Steward C, Hiwarkar P, Saif MA, Hough R, Webb D, et al. Excellent outcome of matched unrelated donor transplantation in paediatric aplastic anaemia following failure with immunosuppressive therapy: a United Kingdom multicentre retrospective experience. *Br J Haematol*. 2012;157:339–436.
  283. Samarasinghe S, Marsh J, Dufour C. Immune suppression for childhood acquired aplastic anaemia and myelodysplastic syndrome: where next? *Haematologica*. 2014;99:597–9.
  284. Dufour C, Veys P, Carraro E, Bhatnagar N, Pillon M, Wynn R, et al. Similar outcome of upfront-unrelated and matched sibling stem cell transplantation in idiopathic paediatric aplastic anaemia. A study on behalf of the UK Paediatric BMT Working Party, Paediatric Diseases Working Party and Severe Aplastic Anaemia Working Party of EBMT. *Br J Haematol*. 2015;171:585–94.
  285. Devillier R, Dalle JH, Kulasekararaj A, D'aveni M, Clément L, Chybicka A, et al. Unrelated alternative donor transplantation for severe acquired aplastic anaemia:

- a study from the French Society of Bone Marrow Transplantation and Cell Therapies and the EBMT Severe Aplastic Anemia Working Party. *Haematologica*. 2016;101:884–90.
286. Burman J, Kirgizov K, Carlson K, Badoglio M, Mancardi GL, De Luca G, et al. Autologous hematopoietic stem cell transplantation for pediatric multiple sclerosis: a registry-based study of the Autoimmune Diseases Working Party (ADWP) and Pediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplant*. 2017;52:1133–7.
  287. Barzaghi F, Amaya Hernandez LC, Neven B, Ricci S, Kucuk ZY, Bleesing JJ, et al. Long-term follow-up of IPEX syndrome patients after different therapeutic strategies: An international multicenter retrospective study. *J Allergy Clin Immunol*. 2018;141:1036–49. e5
  288. Rabusin M, Snowden JA, Veys P, Quartier P, Dalle JH, Dhooge C, et al. Long term outcomes of hematopoietic stem cell transplantation (HSCT) for severe treatment resistant autoimmune cytopenia in children. *Biol Blood Marrow Transplant*. 2013;19:666–9.
  289. Silva J, Ladomenou F, Carpenter B, Chandra S, Sedlacek P, Formankova R, et al. Allogeneic hematopoietic stem cell transplantation for severe, refractory juvenile idiopathic arthritis. *Blood Adv*. 2018;2:777–86.
  290. Medeiros C, Zaris-Neto J, Pasquini R. Bone marrow transplantation for patients with Fanconi anaemia: reduced doses of cyclophosphamide without irradiation as conditioning. *Bone Marrow Transplant*. 1999;24:849–52.
  291. De Latour RP, Porcher R, Dalle J-H, Aljurf M, Korthof ET, Svahn J, et al. Allogeneic haemopoietic stem cell transplantation in Fanconi anaemia: the European Group for Blood and Bone Marrow Transplantation experience. *Blood*. 2013;122:4279–86.
  292. Mehta PA, Davies SM, Leemhuis T, Myers K, Kernan NA, Prockop SE, et al. Radiation-free, alternative-donor HCT for Fanconi anemia patients: results from a prospective multi-institutional study. *Blood*. 2017;129:2308–15.
  293. Fioredda F, Iacobelli S, Korthof ET, Knol C, van Biezen A, Bresters D, et al. Outcome of haematopoietic stem cell transplantation in dyskeratosis congenita. *Br J Haematol*. 2018;183:110–8.
  294. Gadalla SM, Sales-Bonfim C, Carreras J, Alter BP, Antin JH, Ayas M, et al. Outcomes of allogeneic hematopoietic cell transplantation in patients with dyskeratosis congenita. *Biol Blood Marrow Transplant*. 2013;19:1238–43.
  295. Ayas M, Nassar A, Hamidieh AA, Kharfan-Dabaja M, Othman TB, Elhaddad A, et al. Reduced intensity conditioning is effective for hematopoietic SCT in dyskeratosis congenita-related BM failure. *Bone Marrow Transplant*. 2013;48:1168–72.
  296. Fagioli F, Quarello P, Zecca M, Lanino E, Corti P, Favre C, et al. Haematopoietic stem cell transplantation for Diamond Blackfan anaemia: a report from the Italian Association of Paediatric Haematology and Oncology Registry. *Br J Haematol*. 2014;165:673–81.
  297. Tangye SG, Al-Herz W, Bousfiha A, Chatila T, Cunningham-Rundles C, Etzioni A, et al. Human inborn errors of immunity: 2019 update on the classification from the International Union of Immunological Societies Expert Committee. *J Clin Immunol*. 2020;40:24–64.
  298. Lankester AC, Albert MH, Booth C, Gennery AR, Güngör T, Höng M, et al. EBMT/ESID inborn errors working party guidelines for hematopoietic stem cell transplantation for inborn errors of immunity. *Bone Marrow Transplant*. 2021;56:2052–62.
  299. Lum SH, Neven B, Slatter MA, Gennery AR. Hematopoietic cell transplantation for MHC Class II deficiency. *Front Pediatr*. 2019;7:516.
  300. Aydin SE, Freeman AF, Al-Herz W, Al-Mousa HA, Arnaout RK, Aydin RC, et al. Hematopoietic stem cell transplantation as treatment for patients with DOCK8 deficiency. *J Allergy Clin Immunol Pract*. 2019;7:848–55.
  301. Ferrua F, Galimberti S, Courteille V, Slatter MA, Booth C, Moshous D, et al. Hematopoietic stem cell transplantation for CD40 ligand deficiency: Results from an EBMT/ESID-IEWP-SCETIDE-PIDTC study. *J Allergy Clin Immunol*. 2019;143:2238–53.
  302. Ghosh S, Köstel Bal S, Edwards ESJ, Pillay B, Jiménez Heredia R, Erol, et al. Extended clinical and immunological phenotype and transplant outcome in CD27 and CD70 deficiency. *Blood*. 2020;136:2638–55.
  303. Shah RM, Elfeky R, Nademi Z, Qasim W, Amrolia P, Chiesa T, et al. T-cell receptor  $\alpha\beta^+$  and CD19 $^+$  cell-depleted haploidentical and mismatched hematopoietic stem cell transplantation in primary immune deficiency. *J Allergy Clin Immunol*. 2018;141:1417–26. e1
  304. Bertaina A, Merli P, Rutella S, Pagliara D, Bernardo ME, Masetti R, et al. HLA-haploidentical stem cell transplantation after removal of  $\alpha\beta^+$  T and B cells in children with nonmalignant disorders. *Blood*. 2014;124:822–6.
  305. Laberko A, Sultanova E, Gutovskaya E, Shipitsina I, Shelikhova L, Kurnikova E, et al. Mismatched related vs matched unrelated donors in TCR $\alpha\beta$ /CD19-depleted HSCT for primary immunodeficiencies. *Blood*. 2019;134:1755–63.
  306. Neven B, Diana JS, Castelle M, Magnani A, Rosain J, Touzot F, et al. Haplo-identical hematopoietic stem cell transplantation with post-transplant cyclophosphamide for primary immunodeficiencies and inherited disorders in children. *Biol Blood Marrow Transplant*. 2019;25:1363–73.
  307. Folloni Fernandes J, Nichele S, Arcuri LA, Ribeiro L, Zamperlini-Netto G, Loth G, et al. Outcomes after haploidentical stem cell transplantation with post-transplantation cyclophosphamide in patients with primary immunodeficiency diseases. *Biol Blood Marrow Transplant*. 2020;26:1923–9.
  308. Bakhtiar S, Fekadu J, Seidel MK, Gambineri E. Allogeneic hematopoietic stem cell transplantation for congenital immune dysregulatory disorders. *Front Pediatr*. 2019;7:461.
  309. Lehmberg K, Moshous D, Booth C. Haematopoietic stem cell transplantation for primary haemophagocytic lymphohistiocytosis. *Front Pediatr*. 2019;7:435.
  310. Lucchini G, Marsh R, Gilmour K, Worth A, Nademi Z, Rao A, et al. Treatment dilemmas in asymptomatic children with primary hemophagocytic lymphohistiocytosis. *Blood*. 2018;132:2088–96.
  311. Bakhtiar S, Salzmann-Manrique E, Blok HJ, Eikema DJ, Hazelaar S, Ayas M, et al. Allogeneic hematopoietic stem cell transplantation in leukocyte adhesion deficiency type I and III. *Blood Adv*. 2021;5:262–73.
  312. Chiesa R, Wang J, Blok HJ, Hazelaar S, Neven B, et al. Despina Moshous hematopoietic cell transplantation in chronic granulomatous disease: a study of 712 children and adults. *Blood*. 2020;136:1201–11.
  313. Kohn DB, Booth C, Shaw KL, Xu-Bayford J, Garabedian E, Trevisan V, et al. Autologous ex vivo lentiviral gene therapy for adenosine deaminase deficiency. *N Engl J Med*. 2021;384:2002–13.
  314. Kohn DB, Booth C, Kang EM, Pai SY, Shaw KL, Santilli G, et al. Lentiviral gene therapy for X-linked chronic granulomatous disease. *Nat Med*. 2020;26:200–6.
  315. Ferrua F, Cicalese MP, Galimberti S, Giannelli S, Dionisio F, Barzaghi F, et al. Lentiviral haemopoietic stem/progenitor cell gene therapy for treatment of Wiskott-Aldrich syndrome: interim results of a non-randomised, open-label, phase 1/2 clinical study. *Lancet Haematol*. 2019;6:e239–e253.
  316. Tan EY, Boelens JJ, Jones SA, Wynn RF. Hematopoietic stem cell transplantation in inborn errors of metabolism. *Front Pediatr*. 2019;7:433.
  317. Halter JP, Michael W, Schüpbach M, Mandel H, Casali C, Orchard K, et al. Allogeneic hematopoietic stem cell transplantation for mitochondrial neurogastrointestinal encephalomyopathy. *Brain*. 2015;138:2847–58.
  318. Gentner B, Tucci F, Galimberti S, Fumagalli F, De Pellegrin M, Silvani P, et al. Hematopoietic stem- and progenitor-cell gene therapy for Hurler syndrome. *N Engl J Med*. 2021;385(Nov):1929–40.
  319. Federico A, de Visser M. New disease modifying therapies for two genetic childhood-onset neurometabolic disorders (metachromatic leucodystrophy and adrenoleucodystrophy). *Neurol Sci*. 2021;42:2603–6.
  320. Locatelli F, Kabbara N, Ruggeri A, Ghavamzadeh A, Roberts I, Li CK, et al. Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. *Blood*. 2013;122:1072–8.
  321. Gaziev J, Marzali M, Isgro A, Sodani P, Paciaroni K, Gallucci C, et al. Bone marrow transplantation for thalassemia from alternative related donors: improved outcomes with a new approach. *Blood*. 2013;122:2751–6.
  322. Lucarelli G, Isgro A, Sodani P, Gaziev J. Hematopoietic stem cell transplantation in thalassemia and sickle cell anemia. *Cold Spring Harb Perspect Med*. 2012;2:a011825.
  323. Galambun C, Pondarre C, Bertrand Y, Loundou A, Bordigoni P, Frange P, et al. French multicenter 22 year-experience of stem cell transplantation for beta-thalassemia major: lessons and future directions. *Biol Blood Marrow Transplant*. 2013;19:62–68.
  324. Angelucci E, Baronciani D. Allogeneic stem cell transplantation for thalassemia major. *Haematologica*. 2008;93:1780–4.
  325. Li C, Mathews V, Kim S, George B, Hebert K, Jiang H, et al. Related and unrelated donor transplantation for  $\beta$ -thalassemia major: results of an international survey. *Blood Adv*. 2019;3:2562–70.
  326. Anurathapan U, Hongeng S, Pakakasama S, Songdej D, Sirachainan N, Pongpithcha P, et al. Hematopoietic stem cell transplantation for severe thalassemia patients from haploidentical donors using a novel conditioning regimen. *Biol Blood Marrow Transplant*. 2020;26:1106–12.
  327. Vellaichamy Swaminathan V, Ravichandran N, Ramanan KM, Meena SK, Varla H, Ramakrishnan B, et al. Augmented immunosuppression and PTCY-based haplo-identical hematopoietic stem cell transplantation for thalassemia major. *Pediatr Transplant*. 2021;25:e13893.
  328. Oostenbrink LVE, Pool ES, Jol-van der Zijde CM, Jansen-Hoogendijk AM, Vervat C, van Halteren AGS, et al. Successful mismatched hematopoietic stem cell transplantation for pediatric hemoglobinopathy by using ATG and post-transplant cyclophosphamide. *Bone Marrow Transplant*. 2021;56:2203–11.
  329. Matthes-Martin S, Lawitschka A, Fritsch G, Lion T, Grimm B, Breuer S, et al. Stem cell transplantation after reduced-intensity conditioning for sickle cell disease. *Eur J Haematol*. 2013;90:308–12.

330. Lucarelli G, Gaziev J, Isgro A, Sodani P, Paciaroni K, Alfieri C, et al. Allogeneic cellular gene therapy in hemoglobinopathies-evaluation of hematopoietic SCT in sickle cell anemia. *Bone Marrow Transplant.* 2012;47:227–30.
331. Kamani NR, Walters MC, Carter S, Aquino V, Brochstein JA, Chaudhury S, et al. Unrelated donor cord blood transplantation for children with severe sickle cell disease: results of one cohort from the Phase II Study from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). *Biol Blood Marrow Transplant.* 2012;18:1265–72.
332. Cappelli B, Volt F, Tozatto-Maio K, Scigliuolo GM, Ferster A, Dupont S, et al. Risk factors and outcomes according to age at transplantation with an HLA-identical sibling for sickle cell disease. *Haematologica.* 2019;104:e543–e546.
333. Eapen M, Brazauskas R, Walters MC, Bernaudin F, Bo-Subait K, Fitzhugh CD, et al. Effect of donor type and conditioning regimen intensity on allogeneic transplantation outcomes in patients with sickle cell disease: a retrospective multicentre, cohort study. *Lancet Haematol.* 2019;6:e585–e596.
334. de la Fuente J, Dhedin N, Koyama T, Bernaudin F, Kuentz M, Karnik L, et al. Haploidentical bone marrow transplantation with post-transplantation cyclophosphamide plus thiotepa improves donor engraftment in patients with sickle cell anemia: results of an International Learning Collaborative. *Biol Blood Marrow Transplant.* 2019;25:1197–209.
335. Foell J, Schulte JH, Pfirrstinger B, Troeger A, Wolff D, Edinger M, et al. Haplo-identical CD3 or  $\alpha/\beta$  T-cell depleted HSCT in advanced stage sickle cell disease. *Bone Marrow Transplant.* 2019;54:1859–67.
336. Frangoul H, Altshuler D, Cappellini MD, Chen YS, Domm J, Eustace BK, et al. CRISPR-Cas9 gene editing for sickle cell disease and  $\beta$ -thalassemia. *N Engl J Med.* 2021;384:252–60.
337. Sobacchi C, Schulz A, Coxon FP, Villa A, Helfrich MH. Osteopetrosis: genetics, treatment and new insights into osteoclast function. *Nat Rev Endocrinol.* 2013;9:522–36.
338. Snowden JA, McGrath E, Duarte RF, Saccardi R, Orchard K, Worel N, et al. JACIE accreditation for blood and marrow transplantation: past, present and future directions of an international model for healthcare quality improvement. *Bone Marrow Transplant.* 2017;52:1367–71.
339. Gratwohl A, Brand R, Niederwieser D, Baldomero H, Chabannon C, Cornelissen J, et al. Introduction of a quality management system and outcome after hematopoietic stem-cell transplantation. *J Clin Oncol.* 2011;29:1980–6.
340. Gratwohl A, Brand R, McGrath E, van Biezen A, Sureda A, Ljungman P, et al. Use of the quality management system “JACIE” and outcome after hematopoietic stem cell transplantation. *Haematologica.* 2014;99:908–15.
341. Gratwohl A, Sureda A, Baldomero H, Gratwohl M, Dreger P, Kröger N, et al. Macroeconomics and outcome after hematopoietic stem cell transplantation. *E-Biomedicine.* 2015;2:101–9.
342. Schetelig J, de Wreede LC, Andersen NS, Moreno C, van Gelder M, Vitek A, et al. Centre characteristics and procedure-related factors have an impact on outcomes of allogeneic transplantation for patients with CLL: a retrospective analysis from the European Society for Blood and Marrow Transplantation (EBMT). *Br J Haematol.* 2017;178:521–33.
343. Anthias C, Ethell ME, Potter MN, Madrigal A, Shaw BE. The impact of improved JACIE standards on the care of related BM and PBSC donors. *Bone Marrow Transplant.* 2015;50:244–7.
344. Anthias C, O'Donnell PV, Kiefer DM, Yared J, Norkin M, Anderlini P, et al. European Group for Blood and Marrow Transplantation Centers with FACT-JACIE Accreditation have significantly better compliance with related donor care standards. *Biol Blood Marrow Transplant.* 2016;22:514–9.
345. Snowden JA, Saccardi R, Orchard K, Ljungman P, Duarte RF, Labopin M, et al. Benchmarking of survival outcomes following haematopoietic stem cell transplantation: A review of existing processes and the introduction of an international system from the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE). *Bone Marrow Transplant.* 2020;55:681–94.
346. Bazarbachi A, Bug G, Baron F, Brissot E, Ciceri F, Dalle IA, et al. Clinical practice recommendation on hematopoietic stem cell transplantation for acute myeloid leukemia patients with *FLT3*-internal tandem duplication: a position statement from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. *Haematologica.* 2020;105:1507–16.
347. Menon S, Shirani A, Zhao Y, Oger J, Troubsee A, Freedman MS, et al. Characterising aggressive multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2013;84:1192–8.

## ACKNOWLEDGEMENTS

The authors are grateful for the advice and helpful comments received from a number of EBMT fellow specialists in HCT including Michael Albert, Tobias Alexander, Frédéric Baron, Ali Bazarbachi, Meral Beksac, Arianne Boumendil, Tomasz Czrew, Gesine Bug,

Yves Chalandon, Fabio Ciceri, Peter Dreger, Jordi Esteve, Herve Finel, Laurent Garderet, Michel Van Gelder, Sebastian Giebel, Claude Gorin, Patrick J Hayden, Juan Carlos Hernández Boluda, Katharina Kleinschmidt, Francesco Lanza, Donal McLornan, Arnon Nagler, Francesco Onida, Zina Peric, Antonio Risitano, Marie Robin, Giovanni Rosti, Annalisa Ruggeri, Jaime Sanz, Bipin Savani, Christoph Scheid, Christoph Schmid, Norbert Schmitz, Simona Secondino, Stefan Shönland, Roni Shouval, Alexandros Spyridonidis, Olivier Tournilhac, Jurjen Versluis and Robert Wynn.

## AUTHOR CONTRIBUTIONS

JAS and IS-O coordinated the writing of the manuscript following approval of the structure and authorship at the EBMT Board and Scientific Council on 18 June 2021. Relevant sections were drafted by authors designated according to roles within EBMT Scientific Council, Working Parties (WPs) and other roles: namely, SC (Paediatric Diseases WP); MM (Acute Leukaemia WP); IY-A (Chronic Malignancies WP); BG and AS (Lymphoma WP); PP (for Solid Tumours, within Cellular Therapy and Immunobiology WP chaired by CC); RG with JAS (Autoimmune Diseases WP); RPL (Severe Aplastic Anaemia WP, and Inborn Errors WP), with input from ZP and GWB (Transplant Complications WP), RC (Infectious Diseases WP) and JAS (for Quality, JACIE and EBMT Benchmarking). IS-O, RFD, CC, HD, AS and NK provided cross-cutting advisory expertise throughout. JAS and IS-O edited the manuscript and all authors provided input across all sections in the final drafts of the manuscript according to expertise. Other specialists from EBMT are acknowledged. The manuscript was agreed and finalised at the EBMT Board and Scientific Council Meeting on 19 March 2022. All authors approved the final version.

## COMPETING INTERESTS

BG discloses employment and management position by Helios; advisory/expert activity by Roche, Celgene, BMS, Gilead, Janssen, Novartis, Riemser, MSD and Jazz; honoraria by BMS, Celgene, Novartis, Roche, Riemser, Janssen, MSD, Jazz and funding scientific research by Roche, Celgene and Amgen. RG discloses speaking honoraria from educational events supported by Biotech, Pfizer, Medac and Magenta. ACL discloses consultancy and research support by Neovii Biotech. MM discloses honoraria by Adaptive Biotechnologies, Amgen, Astellas, Celgene-BMS, GSK, Gilead, Janssen, Jazz Pharmaceuticals, Novartis, Oncocept, Pfizer, Sanofi, Takeda and research funding by Janssen and Sanofi. RPL discloses expert consultant/speaker's fees by Alexion, Amgen, Gilead, Jazz, Keocyte, MSD, Novartis, Pfizer, Roche, Samsung and Sobi and research grant by Alexion, Amgen, Jazz pharmaceutical, Novartis and Pfizer. AS discloses honoraria by Takeda, BMS/Celgene, MSD, Janssen, Amgen, Novartis, Gilead, Kite, Sanofi, Roche and Alexion; consultancy by Takeda, BMS/Celgene, Novartis, Janssen, Gilead and Sanofi; speaker's bureau by Takeda and research support by Takeda and BMS/Celgene. JAS declares honoraria for educational events from Jazz, Gilead, Janssen, for advisory board membership from Medac, and for trial IDMC membership from Kiadis Pharma. The following authors declare that they have no conflict of interest in this manuscript: IS-O, SC, GWB, CC, RC, HD, RFD, BN, PP, ZP, IY-A and NK.

## ADDITIONAL INFORMATION

**Correspondence** and requests for materials should be addressed to John A. Snowden.

**Reprints and permission information** is available at <http://www.nature.com/reprints>

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/>.

© The Author(s) 2022