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Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation

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A B S T R A C T

Approximately 20,000 hematopoietic cell transplantation (HCT) procedures are performed in the United States annually. With advances in transplantation technology and supportive care practices, HCT has become safer, and patient survival continues to improve over time. Indications for HCT continue to evolve as research refines the role for HCT in established indications and identifies emerging indications where HCT may be beneficial. The American Society for Blood and Marrow Transplantation (ASBMT) established a multiple-stakeholder task force consisting of transplant experts, payer representatives, and a patient advocate to provide guidance on "routine" indications for HCT. This white paper presents the recommendations from the task force. Indications for HCT were categorized as follows: (1) Standard of care, where indication for HCT is well defined and supported by evidence; (2) Standard of care, clinical evidence available, where large clinical trials and observational studies are not available but HCT has been shown to be effective therapy; (3) Standard of care, rare indication, for rare diseases where HCT has demonstrated effectiveness but large clinical trials and observational studies are not feasible; (4) Developmental, for diseases where preclinical and/or early phase clinical studies show HCT to be a promising treatment option; and (5) Not generally recommended, where available evidence does not support the routine use of HCT. The ASBMT will periodically review these guidelines and will update them as new evidence becomes available.

INTRODUCTION

Hematopoietic stem cell transplantation (HCT) using hematopoietic progenitor cells from the patient (autologous HCT) or a donor (allogeneic HCT) is a potentially curative therapy for many life-threatening cancers and nonmalignant disorders. Approximately 20,000 HCTs are performed in the United States each year [1]. The number of annual

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procedures is projected to increase because of several advancements in the field of HCT [2], such as routine use of reduced-intensity conditioning regimens, which allows HCT in older patients who have a high incidence of hematologic malignancies; emerging indications for HCT; and introduction of alternative graft sources such that nearly all patients who need a transplant now have a donor. At the same time, early and long-term HCT outcomes continue to improve with significant improvements in patient selection for HCT, transplantation technology, and preventive and supportive care practices [3-6].

The American Society for Blood and Marrow Transplantation (ASBMT), in response to a need identified by patients, providers, payers, and policymakers, established a Task Force to provide guidance on indications for HCT, that is, which indications may be considered as routine care versus indications where evidence is emerging or insufficient. The Task Force consisted of clinical experts, payers, and patient advocates and was charged with providing consensus guidelines for clinically appropriate indications for HCT based on best prevailing evidence. This white paper presents the recommendations from the Task Force.

GENERAL PRINCIPLES

This article is intended to serve as a guide to the current consensus on the use of HCT to treat a specific indication, both within and external to the clinical trial setting. The Task Force emphasizes that the guidelines should not be used to determine whether HCT should be pursued as a treatment for an individual patient. Whether or not to proceed with transplantation in an individual patient is a clinical decision best made between the patient and his or her provider after a careful consideration of the alternatives, risks, and benefits of the procedure. The Task Force recognizes that most transplant centers have a regular forum (eg, tumor board or patient selection/care conference) where HCT as a treatment option for individual patients is discussed. However, this document may serve as a foundation for discussion among patients, providers, payers, and policymakers regarding coverage for HCT for specific indications.

The following guiding principles were followed by the Task Force in the development of these guidelines:

- The medical decision-making process for a transplant procedure is complex and includes several factors besides the underlying indication for transplantation. Some examples of such variables include patient's overall health and performance status, comorbidities, disease risk/status (eg, remission state and responsiveness to treatment), and graft and donor source. Clinicians routinely consider such factors when evaluating a patient with a specific indication for HCT.
- Recommendations for some diagnoses consider disease risk (eg, cytogenetics inacute myeloid leukemia and acute lymphoblastic leukemia). Disease risk is not defined as a part of this guidance document, and clinicians are instead referred to other guidelines such as those proposed by the National Comprehensive Cancer Network (NCCN; www.nccn.org).
- For the purposes of these guidelines, the definition of HCT as proposed by the ASBMT and the National Marrow Donor Program/Be The Match was followed [7,8]. HCT is defined as an episode of care starting with a preparative regimen and continuing through hematopoietic stem cell infusion and recovery. Hematopoietic stem cell infusion is the infusion of a product (bone marrow, peripheral blood stem cells, cord blood) that contains hematopoietic progenitor cells, often characterized by CD34 expression.
- The European Group for Blood and Marrow Transplantation (EBMT) and the British Society of Blood and Marrow Transplantation (BSBMT) have published recommendations for HCT indications [9,10]. The EBMT and BSBMT guidelines were reviewed in the process of developing ASBMT guidelines.
- The Task Force considered a formal systematic evidence review of the literature but determined that it would not be feasible in the process of formulating our expansive guidelines. Clinical trials and observational studies generally focus on specific questions within a disease or a group of diseases (eg, comparing outcomes in a subset of patients with a disease or investigating approaches for preventing relapse and minimizing morbidity and mortality of transplantation). Extrapolating the evidence to broad indication categories would be challenging. In general, for indications categorized as "Standard of care," "Standard of care, clinical evidence available," or "Standard of care, rare indication" (see below), the level of evidence and consensus was comparable with NCCN category 2A recommendation ("Based upon lower-level evidence, there is uniform consensus that the intervention is appropriate") [11]. All NCCN recommendations are category 2A, unless otherwise noted.
- Where available, published systematic evidence reviews or guidelines were used as the basis for our recommendations for categorizing indications. The ASBMT has published evidence-based reviews for several indications (Table 1). Similarly, other organizations have addressed the use of HCT for various indications (eg, NCCN guidelines and position papers from the ASBMT Practice Guidelines Committee, Center for International Blood and Marrow Transplant Research [CIBMTR] working committees and/or EBMT working parties).
- Overall, the recommendations are based on best available evidence from clinical trials or, where clinical trials are not available, registry, multicenter, or single-center observational studies. A Supplementary Appendix lists key references on individual indications for HCT. Although the list is not exhaustive, the references highlight evidence that was partly used as the basis for our recommendations.
- The guidelines focus on generally agreed on indications for the HCT procedure itself and do not go into other specific aspects of transplantation considered to be

Table 1
List of Evidence-Based Reviews Performed by the ASBMT

Review	Year Published
Acute myeloid leukemia in children [12]	2007
Acute myeloid leukemia in adults [13]	2008
Myelodysplastic syndrome [14]	2009
Follicular lymphoma [15]	2010
Diffuse large B cell lymphoma [16]	2011
Acute lymphoblastic leukemia in children [17]	2012
Acute lymphoblastic leukemia in adults [18]	2012
Multiple myeloma [19]	2015
Hodgkin lymphoma [20]	2015

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beyond the scope of this white paper. We do not provide recommendations on type of conditioning regimen, graft-versus-host disease prophylaxis regimen, donor source, and graft source or recommendations on use of post-HCT maintenance therapy for specific indications. Readers are referred to other published systematic evidence reviews and guidelines for this information.

- The Task Force recommendations are not designed to define comprehensive insurance benefits for HCT. Another ASBMT white paper provides recommendations on defining a standard episode of care for HCT and provides guidance on a general approach to coverage for indications of HCT [8]. Our guidelines can complement the evidence review that payers conduct as part of their technology assessment to determine coverage policies.
- These guidelines will supplement the *Referral Guidelines: Recommended Timing for Transplant Consultation*, developed jointly by the ASBMT and National Marrow Donor Program/Be The Match [21].

RARE DISEASES

Where sufficient evidence from large studies was not available (eg, rare diseases), nonanalytic studies and expert opinion were used, and the recommendations represent prevalent routine clinical practice for those indications. Rather than provide a long and evolving list of unique rare diseases, the indication tables show a concise categorical list together with selected unique diagnoses for which transplant is most frequently offered (Tables 2 and 3). It is recognized that there is a large number of rare disorders for which transplantation may be used, and the appropriateness of HCT may depend on the phenotype and the degree of progression of the disease in an individual patient. To address these scenarios in their entirety is beyond the scope of this report. Gathering additional data in these situations will be important to better understand the benefits and limits of transplantation. Towards this goal and when possible, multi-institutional studies will prove important, preferably in centers with expertise in assessing disease-specific outcomes. For rare indications, providers are advised to discuss with individual patients the risks and benefits of the HCT procedure while considering the available literature and clinical experience.

DONOR AND GRAFT SOURCE IN PATIENT SELECTION FOR HCT

In the present era, a suitable donor source can be found for most patients who may benefit from HCT [22]. Several clinical factors have to be considered when determining the optimal donor and graft source for a given patient, including but not limited to underlying disease, disease stage, and the urgency with which transplantation needs to be pursued. For example, a specific donor and graft source may not be suitable for some patients (eg, umbilical cord blood is not recommended as a donor/graft source for patients with myelofibrosis unless pursued as part of a clinical trial). Although HLA-identical sibling donor remains the preferred donor source, survival after transplantation is comparable among patients receiving hematopoietic progenitor cells from HLA-identical sibling and matched unrelated donors for several diseases [23-31]. Similarly, studies show that survival after umbilical cord blood transplantation is similar to other graft sources, and emerging data demonstrate acceptable outcomes with haploidentical donor transplantation [32-41].

The literature on donor and graft sources continues to evolve rapidly over time. With this background, the Task Force did not differentiate recommendations for transplant indications based on donor source (ie, related donor, unrelated donor, umbilical cord blood, or haploidentical donor) or graft source (ie, bone marrow, peripheral blood stem cells, or umbilical cord blood). This is in contrast to guidelines published by the EBMT and BSBMT. Nonetheless, the Task Force recognizes that donor and graft sources are important considerations when determining the risks and benefits of HCT for an individual patient.

AGE IN PATIENT SELECTION FOR HCT

Age by itself should not be a contraindication to transplantation in patients who may benefit from this procedure. Selected older patients with limited comorbidities and good functional status can safely receive HCT with a relatively low and acceptable risk of nonrelapse mortality [42-44]. Instead of chronologic patient age, evaluations such as functional status, HCT-specific comorbidity index score, EBMT risk score, and Pre-transplantation Assessment of Mortality risk score can assist in determining risks of nonrelapse mortality and transplant candidacy for individual patients.

DEFINITIONS FOR CLASSIFYING INDICATIONS

The definitions for categorizing indications for transplantation are presented below. Tables 2 and 3 list the recommendations for HCT in pediatric and adult diseases.

Standard of Care (S)

This category includes indications that are well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies (eg, through the CIBMTR or EBMT).

Standard of Care, Clinical Evidence Available (C)

This category includes indications for which large clinical trials and observational studies are not available. However, HCT has been shown to be an effective therapy with acceptable risk of morbidity and mortality in sufficiently large single- or multicenter cohort studies. HCT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits. As more evidence becomes available, some indications may be reclassified as “S.”

Standard of Care, Rare Indication (R)

Indications included in this category are rare diseases for which clinical trials and observational studies with sufficient number of patients are not currently feasible because of their very low incidence. However, single- or multicenter or registry studies in relatively small cohorts of patients have shown HCT to be effective treatment with acceptable risks of morbidity and mortality. For patients with diseases in this category, HCT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits.

Developmental (D)

Developmental indications include diseases where preclinical and/or early phase clinical studies show HCT to be a promising treatment option. HCT is best pursued for these indications as part of a clinical trial. As more evidence becomes available, some indications may be reclassified as “C” or “S.”

Table 2
Indications for HCT in Pediatric Patients (Generally Age < 18 years)

Indication and Disease Status	Allogeneic HCT	Autologous HCT
Acute myeloid leukemia		
CR1, low risk	N	N
CR1, intermediate risk	C	N
CR1, high risk	S	N
CR2+	S	N
Not in remission	C	N
Acute promyelocytic leukemia, relapse	R	R
Acute lymphoblastic leukemia		
CR1, standard risk	N	N
CR1, high risk	S	N
CR2	S	N
CR3+	C	N
Not in remission	C	N
Chronic myeloid leukemia		
Chronic phase	C	N
Accelerated phase	C	N
Blast phase	C	N
Myelodysplastic syndromes		
Low risk	C	N
High risk	S	N
Juvenile myelomonocytic leukemia	S	N
Therapy related	S	N
T cell non-Hodgkin lymphoma		
CR1, standard risk	N	N
CR1, high risk	S	N
CR2	S	N
CR3+	C	N
Not in remission	C	N
Lymphoblastic B cell non-Hodgkin lymphoma (non-Burkitt)		
CR1, standard risk	N	N
CR1, high risk	S	N
CR2	S	N
CR3+	C	N
Not in remission	C	N
Burkitt's lymphoma		
First remission	C	C
First or greater relapse, sensitive	C	C
First or greater relapse, resistant	C	N
Hodgkin lymphoma		
CR1	N	N
Primary refractory, sensitive	C	C
Primary refractory, resistant	C	N
First relapse, sensitive	C	C
First relapse, resistant	C	N
Second or greater relapse	C	C
Anaplastic large cell lymphoma		
CR1	N	N
Primary refractory, sensitive	C	C
Primary refractory, resistant	C	N
First relapse, sensitive	C	C
First relapse, resistant	C	N
Second or greater relapse	C	C
Solid tumors		
Germ cell tumor, relapse	D	C
Germ cell tumor, refractory	D	C
Ewing's sarcoma, high risk or relapse	D	S
Soft tissue sarcoma, high risk or relapse	D	D
Neuroblastoma, high risk or relapse	D	S
Wilms' tumor, relapse	N	C
Osteosarcoma, high risk	N	C
Medulloblastoma, high risk	N	C
Other malignant brain tumors	N	C
Nonmalignant diseases		
Severe aplastic anemia, new diagnosis	S	N
Severe aplastic anemia, relapse/refractory	S	N
Fanconi's anemia	R	N
Dyskeratosis congenita	R	N
Blackfan-Diamond anemia	R	N
Sickle cell disease	C	N
Thalassemia	S	N
Congenital amegakaryocytic thrombocytopenia	R	N
Severe combined immunodeficiency	R	N
T cell immunodeficiency, SCID variants	R	N
Wiskott-Aldrich syndrome	R	N
Hemophagocytic disorders	R	N
Lymphoproliferative disorders	R	N
Severe congenital neutropenia	R	N
Chronic granulomatous disease	R	N
Other phagocytic cell disorders	R	N
IPEX syndrome	R	N
Juvenile rheumatoid arthritis	D	R
Systemic sclerosis	D	R
Other autoimmune and immune dysregulation disorders	R	N
Mucopolysaccharoidoses (MPS-I and MPS-VI)	R	N
Other metabolic diseases	R	N
Osteopetrosis	R	N
Globoid cell leukodystrophy (Krabbe)	R	N
Metachromatic leukodystrophy	R	N
Cerebral X-linked adrenoleukodystrophy	R	N

N indicates not generally recommended; C, standard of care, clinical evidence available; S, standard of care; R, standard of care, rare indication; D, developmental; CR1, first complete response; CR2, second CR; CR3, third CR; SCID, Severe combined immunodeficiency; IPEX, Immune dysregulation, polyendocrinopathy, enteropathy, X-linked; MPS, mucopolysaccharidosis.
Rather than provide a long and evolving list of unique rare diseases, this table shows a concise categorical list together with selected unique diagnoses for which transplant is most frequently offered. See text for definition of recommendation categories.

Not Generally Recommended (N)

Transplantation is not currently recommended for these indications where evidence and clinical practice do not support the routine use of HCT. The effectiveness of non-transplant therapies for an earlier phase of a disease does not justify the risks of HCT. Alternatively, a meaningful benefit is not expected from the procedure in patients with an advanced phase of a disease. However, this recommendation does not preclude investigation of HCT as a potential treatment, and transplantation may be pursued for these indications within the context of a clinical trial.

DATA REPORTING TO CIBMTR

US transplant centers report clinical and outcomes data on all allogeneic HCT procedures, and most centers report data on autologous HCT procedures to the CIBMTR. This data reporting and capture is critical to understanding appropriate indications for HCT and its utilization and patient outcomes.

PROCESS FOR UPDATING GUIDELINES

The Task Force recognizes the need for periodically updating these guidelines to keep abreast with ongoing research in the field. New evidence may result in inclusion of new indications not previously recognized or may lead to reclassification of recommendation category for an existing indication. The ASBMT's Practice Guidelines Committee will periodically review these guidelines and update them as necessary, with a minimum of once every 2 years.

PUBLIC COMMENTS

The draft manuscript was reviewed by the ASBMT's Practice Guidelines Committee and was posted on ASBMT's

Table 3
Indications for HCT in Adults (Generally Age ≥ 18 years)

Indication and Disease Status	Allogeneic HCT	Autologous HCT
Acute myeloid leukemia		
CR1, low risk	N	C
CR1, intermediate risk	S	C
CR1, high risk	S	C
CR2	S	C
CR3+	C	C
Not in remission	C	N
Acute promyelocytic leukemia		
CR1	N	N
CR2, molecular remission	C	S
CR2, not in molecular remission	S	N
CR3+	C	N
Not in remission	C	N
Relapse after autologous transplant	C	N
Acute lymphoblastic leukemia		
CR1, standard risk	S	C
CR1, high risk	S	N
CR2	S	C
CR3+	C	N
Not in remission	C	N
Chronic myeloid leukemia		
Chronic phase 1, TKI intolerant	C	N
Chronic phase 1, TKI refractory	C	N
Chronic phase 2+	S	N
Accelerated phase	S	N
Blast phase	S	N
Myelodysplastic syndromes		
Low/intermediate-1 risk	C	N
Intermediate-2/high risk	S	N
Therapy-related AML/MDS		
CR1	S	N
Myelofibrosis and myeloproliferative diseases		
Primary, low risk	C	N
Primary, intermediate/high risk	C	N
Secondary	C	N
Hypereosinophilic syndromes, refractory	R	N
Plasma cell disorders		
Myeloma, initial response	D	S
Myeloma, sensitive relapse	C	S
Myeloma, refractory	C	C
Plasma cell leukemia	C	C
Primary amyloidosis	N	C
POEMS syndrome	N	R
Relapse after autologous transplant	C	C
Hodgkin lymphoma		
CR1 (PET negative)	N	N
CR1 (PET positive)	N	C
Primary refractory, sensitive	C	S
Primary refractory, resistant	C	N
First relapse, sensitive	S	S
First relapse, resistant	C	N
Second or greater relapse	C	S
Relapse after autologous transplant	C	N
Diffuse large B cell lymphoma		
CR1 (PET negative)	N	N
CR1 (PET positive)	N	C
Primary refractory, sensitive	C	S
Primary refractory, resistant	C	N
First relapse, sensitive	C	S
First relapse, resistant	C	N
Second or greater relapse	C	S
Relapse after autologous transplant	C	N
Follicular lymphoma		
CR1	N	C
Primary refractory, sensitive	S	S
Primary refractory, resistant	S	N
First relapse, sensitive	S	S
First relapse, resistant	S	N
Second or greater relapse	S	S
Transformation to high grade lymphoma	C	S
Relapse after autologous transplant	C	N
Mantle cell lymphoma		
CR1/PR1	C	S
Primary refractory, sensitive	S	S
Primary refractory, resistant	C	N
First relapse, sensitive	S	S
First relapse, resistant	C	N
Second or greater relapse	C	S
Relapse after autologous transplant	C	N
T cell lymphoma		
CR1	C	C
Primary refractory, sensitive	C	S
Primary refractory, resistant	C	N
First relapse, sensitive	C	S
First relapse, resistant	C	N
Second or greater relapse	C	C
Relapse after autologous transplant	C	N
Lymphoplasmacytic lymphoma		
CR1	N	N
Primary refractory, sensitive	N	C
Primary refractory, resistant	R	N
First or greater relapse, sensitive	R	C
First or greater relapse, resistant	R	N
Relapse after autologous transplant	C	N
Burkitt's lymphoma		
First remission	C	C
First or greater relapse, sensitive	C	C
First or greater relapse, resistant	C	N
Relapse after autologous transplant	C	N
Cutaneous T cell lymphoma		
Relapse	C	C
Relapse after autologous transplant	C	N
Plasmablastic lymphoma		
CR1	R	R
Relapse	R	R
Chronic lymphocytic leukemia		
High risk, first or greater remission	C	N
T cell prolymphocytic leukemia	R	R
B cell, prolymphocytic leukemia	R	R
Transformation to high grade lymphoma	C	C
Solid tumors		
Germ cell tumor, relapse	N	C
Germ cell tumor, refractory	N	C
Ewing's sarcoma, high risk	N	C
Breast cancer, adjuvant high risk	N	D
Breast cancer, metastatic	D	D
Renal cancer, metastatic	D	N
Nonmalignant diseases		
Severe aplastic anemia, new diagnosis	S	N
Severe aplastic anemia, relapse/refractory	S	N
Fanconi's anemia	R	N
Dyskeratosis congenita	R	N
Sickle cell disease	C	N
Thalassemia	D	N
Hemophagocytic syndromes, refractory	R	N
Mast cell diseases	R	N
Common variable immunodeficiency	R	N
Wiskott-Aldrich syndrome	R	N
Chronic granulomatous disease	R	N
Multiple sclerosis	N	D
Systemic sclerosis	N	D
Rheumatoid arthritis	N	D
Systemic lupus erythematosus	N	D
Crohn's disease	N	D
Polymyositis-dermatomyositis	N	D

TKI indicates tyrosine kinase inhibitor; AML/MDS, acute myelogenous leukemia/myelodysplastic syndrome; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes; PET, positron emission tomography; PR1, first partial response.
Rather than provide a long and evolving list of unique rare diseases, this table shows a concise categorical list together with selected unique diagnoses for which transplant is most frequently offered. See text for definition of recommendation categories.

website for public comments. The document was modified based on feedback received by the ASBMT community.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at 10.1016/j.bbmt.2015.07.032. The Supplementary Appendix includes a bibliography that lists key publications that support the Task Force recommendations. An up-to-date version of the guidelines and bibliography supporting the recommendations is available at the ASBMT's website (www.asbmt.org/?page=GuidelineStatements).

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