Guidelines for

Indication of Bone Marrow Transplant for Hematological Disorders

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ARMED FORCES BONE MARROW TRANSPLANT CENTRE/NATIONAL INSTITUTE OF BLOOD AND MARROW TRANSPLANT

INDICATIONS OF HSCT VER1.22

Classification of Indication(1)

Classification	Definition	Action
Standard of care(S)	Supported by evidence in the form of high-quality clinical trials and/or observational studies (eg, through CIBMTR or European Society for Blood and Marrow Transplantation.	Enroll for transplant after discussion in transplant meeting
Clinical evidence available(C)	Large clinical trials and observational studies are not available. However, HSCT has been shown to be an effective therapy with acceptable risk of morbidity and mortality in sufficiently large single-center or multicenter cohort studies. HCT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits.	To be discussed in departmental meeting for transplant eligibility based on case-to-case basis
Rare indication(R)	Clinical trials and observational studies with sufficient number of patients are not currently feasible because of their very low incidence. HSCT has been shown to be an effective therapy with acceptable risk of morbidity and mortality in sufficiently large single-center or multicenter cohort studies. HCT/IECT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits.	To be discussed in departmental meeting for transplant eligibility based on case-to-case basis
Developmental(D)	Preclinical and/or early-phase clinical studies show HSCT to be a promising treatment option. HSCT is best pursued for these indications as part of a clinical trial	To be discussed in MDT /departmental meetings for transplant eligibility based on case-to-case basis
Not recommended(N)	Current evidence does not support the routine use.	Rejection after discussion in departmental meeting

Indication and disease status	MRD HSCT		Haplo-HSCT for those lacking MRD		Autologous HSCT	
	Indication	Age (year)	Indication	Age limit	Indication	Age (year)
NSAA (Refractory/life threatening bleeding, recurrent infections, high transfusion requirement)	S	≤55	D	≤45	N	
SAA/VSAA	S	≤55	C	≤45	N	
Fanconi anemia						
SAA/VSAA	S		N		N	
MDS	D		N		N	
AML	D		N		N	
Thalassemia	S	≤10	N		N	
Acute myeloid leukemia[2]		≤50		≤45		
CR1, Favorable risk (MRD-ve)	N		N		N	
CR1, Favorable risk (MRD+ve)	S		S		D	
CR1, Int-risk	S		C		C	
CR1, High risk/t-AML	S		S		N	
CR2+	S		S		N	
Not in remission	N		N		N	
Acute promyelocytic leukemia		**≤50**		**≤45**		
CR1	**N**		**N**		**N**	
CR2, molecular remission	**N**		**N**		**S**	
CR2, not in molecular remission	**S**		**C**		**N**	
CR3+	**S**		**C**		**N**	
Not in remission	**N**		**N**		**N**	

Relapse after auto-HSCT	**S**		**C**		**N**	
Acute lymphoblastic leukemia (AYA 15-34 years)- Treated with Pediatric protocol						
CR1, Standard risk (MRD -ve)	**N**		**N**		**N**	
CR1, Standard risk (MRD +ve, MRD NA)	**S**		**C**		**N**	
CR1, High risk	**S**		**C**		**N**	
CR2	**S**		**C**		**N**	
Not in remission	**N**		**N**		**N**	
Acute lymphoblastic leukemia (Adults ≥35 years	**Age <50**		**Age<45**			
CR1, Standard risk (MRD -ve)	**C**		**N**		**N**	
CR1, Standard risk (MRD +ve, MRD NA)	**S**		**C**		**N**	
CR1, High risk	**S**		**C**		**N**	
CR2	**S**		**C**		**N**	
Not in remission	**N**		**N**		**N**	
MDS		**<50**		**<40**		
Low/int-risk	**C**		**N**		**N**	
High risk	**S**		**D**		**N**	
Myelofibrosis		**<45**		**<40**		
Primary, low risk	**N**		**N**		**N**	
Primary, high risk	**C**		**N**		**N**	
Secondary	**D**		**N**		**N**	
Multiple myeloma						**<65**
CR, sCR, MRD -ve CR	**N**		**N**		**S**	

PR, VGPR (after best salvage)	N		N		C	
Refractory myeloma	N		N		N	
Relapsed post auto-HSCT	C (<50)		N		C	
AL Amyloidosis	N		N		S	<65
Plasma cell leukemia	C	<50	N		S	<65
POEMS syndrome	N		N		C	<65
Hodgkin lymphoma		<50		<45		<60
CR1	N		N		N	
Relapsed/refractory, CR post salvage	N		N		S	
Relapsed/refractory, PR post salvage	N		N		C	
Refractory post salvage	N		N		N	
Relapsed post auto-HSCT	S		D		N	
Relapsed/refractory with stem cell mobilization failure	S		D		N	
Diffuse large -B cell lymphoma/DHL/RS		<50		<45		<60
CR1	N		N		N	
Relapsed refractory, CR post salvage	N		N		S	
Relapsed refractory, PR post salvage	N		N		C	
Relapsed refractory, resistant post salvage	N		N		N	
Relapse post autologous HSCT	C		D		N	
Primary CNS lymphoma		<45				<50
CR1	N		N		S	
Relapse, CR post salvage	N		N		S	
Relapsed post Auto HSCT	C		N		N	
Follicular lymphoma		<50		<45		<60

CR1	N		N		N	
Relapsed refractory, CR/PR post salvage	N		N		C	
Relapse post autologous HSCT	C		D		N	
High grade transformation	C		D		S	
Mantle cell lymphoma		<50		<45		<60
CR1/PR	N		N		S	
Relapsed refractory, CR post salvage	N		N		S	
Relapse post autologous HSCT	S		D		N	
T-cell lymphoma		<50		<45		<60
CR1	N		N		S	
Relapsed refractory, CR post salvage	N		N		S	
Relapse post autologous HSCT	S		D		N	
Waldenstorm macroglobulinemia		<50		<45		<60
CR1	N		N		N	
Relapsed refractory, CR post salvage	N		N		C	
Relapse post autologous HSCT	D		D		N	
Burkitt lymphoma		<50		<45		<60
CR1	N		N		N	
Relapsed refractory, CR post salvage	N		N		S	
Relapse post autologous HSCT	S		D		N	
Cutaneous T cell lymphoma		<50		<45		<60
CR1	N		N		N	
Relapsed	N		N		C	
Plasmablastic lymphoma		<50		<45		<60

CR1	N		N		N	
Relapsed	R		N		C	
Chronic lymphocytic leukemia		<50		<45		<60
High risk multi-relapsed,	C		N		N	
T-PLL	C		N		N	
B-PLL	C		N		D	
High grade transformation	C		N		S	
Chronic Myeloid Leukemia		<50		<45		
Chronic Phase 1, 2G TKI intolerant/refractory	S		N		N	
Chronic Phase 2	S		N		N	
Accelerated Phase	S		N		N	
Blast Crisis	S		C		N	
Younger pts for whom TKI not affording	S		N		N	
Hairy cell leukemia	N		N		N	
Germ cell tumor						
CR1	N		N		N	
Relapsed refractory	N		N		D	
SCID	S		C		N	
Severe congenital neutropenia	S		C		N	
Chronic granulomatous disease	S		C		N	
DKC	S		D		N	
Sickle cell anemia (fulfilling HSCT criteria)	S		N		N	
HLH (primary, secondary relapsed refractory)	S		C		N	

CVID	**S**		**C**		**N**	
CGD	**S**		**C**		**N**	
Multiple sclerosis	**N**	**-**	**N**	**-**	**C**	**<50**
Systemic Sclerosis	**N**	**-**	**N**	**-**	**N**	**<50**
Rheumatoid arthritis	**N**	**-**	**N**	**-**	**N**	**<50**
SLE	**N**		**N**		**N**	**<50**
Crohns disease	**N**		**N**		**N**	**<50**
Polymyositis/DM	**N**		**N**		**N**	**<50**
Osteopetrosis	**D**		**N**		**N**	
X-linked cerebral leukodystrophy	**N**		**N**		**N**	

1. Kanate AS, Majhail NS, Savani BN, Bredeson C, Champlin RE, Crawford S, et al. Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy: Guidelines for Hematopoietic Transplantation and Cellular Therapy. Biology of Blood and Marrow Transplantation. 2020.

Discussion

1. **HSCT in AML**

   Ref 2. the ELN group recommend consideration of allo-SCT in fit adults with AML in CR1 who have a predicted relapse risk of 35-40% and a suitable donor . Thus adults with AML in CR1 who fulfill ELN criteria for good risk disease on the basis of cytogenetics or the presence of an NPM1 mutation without FLT3-ITD mutation, and demonstrate a good response to induction chemotherapy by MRD criteria are not routinely deemed eligible for an allo-SCT in CR1. Conversely, all other adults in CR1 in whom the predicted risk of relapse of >40% if they are treated with IC alone should, in principle, be considered transplant candidates providing a suitable stem cell donor is available (https://www.frontiersin.org/articles/10.3389/fimmu.2021.659595/full#f1)

2. HSCT in ALL

HLA typing and BMT referral should be considered for all newly diagnosed patients for timely donor identification and ultimately allo-HSCT if warranted.In UK MRC XIII trial, In this setting, when restricting the analysis to Ph (-) ALL, the availability of a matched sibling donor was associated with the superior overall survival reported at 53% versus 45% at 5 years, (p = 0.01). This survival difference was seen in patients with standard risk ALL (deined by age and molecular characteristics), but not in high-risk patients due to increased nonrelapse mortality (NRM) of 36% observed at 2 years. Also importantly, chemotherapy was found to be superior to autologous HCT with a higher 5-year overall survival (OS) rate (46% vs 37%,p = 0.03.)The PETHEMA ALL-AR03 trial identified patients with high-risk Ph(–) ALL and assigned patients to HCT based upon the presence or absence of MRD after consolidation. Current recommendations support the use of pediatric-inspired intensive induction regimens in the AYA. Population (uptill 40 years, CALGB 10403) to gain MRD negative status and in that case, continue with chemotherapy Consolidation and maintenance. .Allogeneic HCT in the AYA population shall be reserved for those patients with persistent MRD and for the small subset of patients with high-risk features.

Ph+ve ALL:

Induction chemotherapy including a TKI followed by allogeneic HCT leads to OS of 50–70% at 2–4 years, and therefore has been considered

SOC in transplant eligible patients. Most recently, an update of the prior report by Jabbour et al. was reported on the combination of hyper-CVAD alternating with high-dose methotrexate/ cytarabine in combination with ponatinib as frontline therapy for ALL. Excellent outcomes were seen with an OS of 73% and CMR rate of 84%. For patients not undergoing allogeneic HCT in CR1, a 3-year OS rate of 90% was seen , suggesting that nontransplant approaches could evolve to be a new SOC with confirmation needed in phase III randomized trials. Proceeding to HSCT with MRD positive for Ph-chromosome is not recommended and MRD-ve status should be achieved with additional chemotherapy/blinatumomab/alternate TKI. In younger pts <21 years there is emerging data to support use of TKI+Chemotherapy over HSCT (Shultz et al 2009, NCCN 2021).