

* CHAPTER 17

Indications and current practice for allogeneic and autologous HSCT for haematological diseases, solid tumours and immune disorders

P. Ljungman, A. Gratwohl for the European Group
for Blood and Marrow Transplantation

1. Introduction

The EBMT has since 1996 regularly published special reports on the indications for and current practice of haematopoietic stem cell transplantation (HSCT) in Europe for congenital or acquired haematological diseases, solid tumours, immune disorders and inborn errors of metabolism (1–4). Major changes have occurred since the first report was published. Today, approximately 25,000 transplants (10,000 allogeneic and 15,000 autologous) are performed yearly by teams reporting to the annual EBMT survey (Table 1). Autologous and allogeneic HSCT are now established treatment options and have been incorporated into the treatment algorithms for many disorders. In addition, potential new indications have emerged such as autoimmune disorders and AL amyloidosis for autologous transplants and solid tumours for allogeneic transplants. Carefully conducted prospective studies hopefully will define the role of HSCT in these situations. On the other hand alternative non-transplant based treatment options are also making major progress, thus influencing the practice of HSCT. For example the number of transplants for previously important indications such as chronic myeloid leukaemia (CML) has been reduced with the introduction of the tyrosine kinase inhibitors. Furthermore, the technical developments made during the last decade have been impressive. Unrelated donor pools have expanded and alternative donors are now more extensively used. Stem cell sources include bone marrow, peripheral blood and cord blood. It is evident that recommendations are based on an ever-changing field. Long-term follow up is lacking for recently introduced methods, while available long term observations may relate to technologies no longer in use today. Still, a few principles remain valid.

2. Risk factors for transplant outcome

The main risk factors for outcome can be defined today. They are based on stage of the disease, age of the patient, time interval from diagnosis to transplant and, for allogeneic HSCT, donor-recipient histocompatibility and donor-recipient sex combination. These risk factors are cumulative and can be modified by additional particularly good or poor prognostic features as exemplified in Table 2. The importance for outcome of this type of risk assessment has been shown for CML (5) and similar evaluations are in process for other diseases. In general, transplant related mortality increases and survival rates decrease with advanced disease stage, increasing age, increasing time from diagnosis to transplant, increasing histoincompatibility and in grafts involving male recipients with a female donor. All components have to be integrated into the risk assessment and the decision whether or not to perform a transplant. These factors are never absolute, for example, the age of an individual patient remains one of the most important determinants of

Table 1: Number of patients treated with a first HSCT by indication, donor type and stem cell source

TEAMS = 605	Allogeneic							
	Family							
	HLA-id			non-id			twin	
	BM	PBPC	Cord	BM	PBPC	Cord	BM	PBPC
Leukaemias	793	2449	14	46	300	2	5	2
Acute myeloid leukaemia	275	1248	4	20	166		0	1
1st complete remission	198	834	2	8	48			1
not 1st complete remission	77	414	2	12	118			0
Acute lymphatic leukaemia	310	433	6	17	67	2	2	5
1st complete remission	189	271	3	5	17	2	1	2
not 1st complete remission	121	162	3	12	50		1	3
Chronic myeloid leukaemia	99	237	0	3	16	0	0	2
chronic phase	73	163		2	4			2
not 1st chronic phase	26	74		1	12			0
MDS incl. Sec AL	83	286	2		36		1	1
MPS	21	93	2	5	10		2	1
Chronic lymphatic leukaemia	5	152		1	5			1
Lymphoproliferative disorders	88	790	0	4	48	0	2	8
Plasma cell disorders - MM	20	255		1	8		2	3
Plasma cell disorders - other	3	7		1				1
Hodgkin's lymphoma	14	120		1	15			1
Non Hodgkin lymphoma	51	408		1	25			5
Solid tumors	13	29	2	1	22	0	3	6
Neuroblastoma	7	1	2	1	9		2	1
Soft tissue sarcoma	1	1			7		1	
Germinal tumours		1			1			
Breast cancer		8			4			
Ewing	2	2						
Renal cancer		6						
Melanoma		2						
Colon cancer								
Other solid tumours	3	8			1			
Non malignant disorders	399	195	29	47	64	2	1	1
Bone marrow failure - SAA	164	100	3	6	6		1	1
Bone marrow failure - other	32	21	3	4	4			
Haemoglobinopathies - thal	92	52	19	7	12			
Haemoglobinopathies - other	26	7	1		1			
Immune deficiencies	64	9	2	19	35	2		
Inherited disorders of metabolism	19	3	1	11	6			
Auto immune disease	2	3						
Others	17	20		1	2			
TOTAL	1310	3483	45	99	436	4	11	3

and stem cell source in Europe in 2006

DONOR SOURCE											
No. of patients											
Donor	Allogeneic					Autologous			Total		
	twin		Unrelated			BM only	BM + PBPC	Cord	Allo	Auto	Total
	BM	PBPC	BM	PBPC	Cord						
	5	23	646	2181	325	78	1101	0	6784	1179	7963
	0	15	237	913	142	64	747	0	3020	811	3831
		10	111	379	54	49	632		1644	681	2325
		5	126	534	88	15	115		1376	130	1506
	2	5	255	464	129	6	145	0	1690	151	1841
	1	2	125	249	56	3	93		920	96	1016
	1	3	130	215	73	3	52		770	55	825
	0	2	57	196	10	0	13	0	620	13	633
		2	40	87	2		4		373	4	377
			17	109	8		9		247	9	256
	1	1	63	363	31	1	37		866	38	904
	2		24	130	7		9		294	9	303
			10	115	6	7	150		294	157	451
	2	8	69	554	34	95	12477	0	1597	12572	14169
	2	3	13	184	3	20	5918		489	5938	6427
			4			1	251		15	252	267
			17	85	8	28	1742		260	1770	2030
		5	39	281	23	46	4566		833	4612	5445
	3	0	4	10	1	77	1402	0	85	1479	1564
	2		3			37	295		25	332	357
	1					9	63		10	72	82
			1	1		7	299		4	306	310
			3				134		15	134	149
			3			9	237		7	246	253
			2			1	7		8	8	16
									2	0	2
							5		0	5	5
			1	1		14	362		14	376	390
	1	1	195	93	89	5	122	0	1115	127	1242
	1	1	59	36	14				390	0	390
			21	16	15				116	0	116
			19	6	1	1	2		208	3	211
			4						39	0	39
			69	23	35	3			258	3	261
			18	9	23		2		90	2	92
			5	3	1	1	118		14	119	133
			18	13	9	1	31		80	32	112
	11	32	932	2851	458	256	15133	0	9661	15389	25050

Table 2: Quantification of risk of transplant-related mortality

Disease stage		
- Early (e.g. AML CR1)		0
- Intermediate (e.g. AML CR2)		1
- Advanced (e.g. refractory disease)		2
Age of patient		
- <20 yr		0
- 20-40 yr		1
- >40 yr		2
Time interval diagnosis to transplant		
- >12 months		0
- >12 months (does not apply to patients in CR1)		1
Histocompatibility		
- HLA-identical sibling		0
- Other donor		1
Gender combination		
- Other		0
- Female donor for male recipient		1
Additional elements		
- Comorbidity / Karnofsky <80	add	+1
- Donor >50 years	add	+1
- CMV not +/-	add	+1
- Syngeneic twin		-1
- Unrelated donor 10/10 high resolution matched		-1

outcome following both allogeneic and autologous HSCT-procedures. Generally, HSCT in children gives better results than in adults. Age cannot be seen as a single risk factor but must be taken together with other factors in the decision-making regarding HSCT. It should, however, be recognised that biological rather than chronological age is the more important determining factor for outcome and with reduced intensity conditioning regimens in allogeneic transplantation, the age limit has increased, permitting the inclusion of older patients.

3. The EBMT recommendations

The EBMT recommendations are based on existing prospective clinical trials, EBMT registry data, and expert opinions. They are not formal evidence-based documents. Many potential indications are rare and will never be supported by evidence from an adequately powered randomised controlled trial.

In addition, since thousands of patients survive long-term, issues of quality of life and late side effects are becoming increasingly important. This is especially

important in children for whom late effects, such as growth retardation, sterility, impairment of intellectual ability, and secondary tumours have an even larger impact than in adults. It is, therefore, important when recommendations are made to integrate the possible survival gain from HSCT, the risk for late complications and the quality of life into the risk assessment strategy. Some recommendations were made based upon analogy, inference, and expertise. However, there is increasing knowledge from a number of well-designed prospective studies that have used standard randomisation procedures or the so called genetic randomisation technique. In the future, EBMT recommendations will incorporate evidence assessed in a more formal way. The EBMT recommendations are not meant to decide whether a transplant is the correct choice of procedure or not for an individual patient. They give guidance which must be considered together with the risk of the disease, the risk of the transplant procedure and the chances of strategies in the same situation.

3.1. Conditioning regimens

Conditioning regimens vary in their intensity and are classified as standard intensity conditioning, reduced intensity conditioning, or intensified conditioning regimens. Reduced intensity conditioning (RIC) regimens can be used in the allogeneic setting with the intention of shifting the balance between risk of transplant-related mortality and risk of relapse. During recent years approximately one quarter of all allogeneic HSCT were performed with RIC regimens. A wide variety of RIC regimens have been described in publications and RIC HSCT should preferably be performed with a previously published protocol to gain adequate experience with a few protocols. Extensive feasibility studies have been published and short-term results show that RIC HSCT can lower the risk for early transplant related mortality. This has been used as the main argument to use RIC HSCT for older patients and for patients with co-morbidities. Results have been published for related donor HSCT up to 75 years and for unrelated donor HSCT up to 70 years. The preferred stem cell source has been peripheral blood (90%). Experience with unrelated donors has been published with results comparable to those with related donors. No formal prospective or retrospective studies however, have so far shown superior long-term results with RIC HSCT compared to standard HSCT. A conventional transplant remains the therapy of choice for younger patients without co-morbidities in the absence of results from prospective, controlled trials.

3.2. Classification of indications

An important aim of the indication documents has been to classify indications and to give advice about the settings in which these various types of transplants should be performed. They have been classified as "standard of care", "clinical option",

“developmental” or “generally not recommended”. Respective examples are given in Table 3.

Table 3: Examples of transplant categories

Standard of care	- AML CR2, allogeneic HSCT - Multiple myeloma, autologous HSCT
Clinical option	- Non-Hodgkin lymphoma, allogeneic HSCT
Developmental	- Autoimmune disease, autologous HSCT
Not recommended	- CML, blast crisis

3.2.1. “Standard of care”

“Standard of care” transplants may be performed in any specialist centre with experience with HSCT procedures provided they have an appropriate infrastructure as defined by the EBMT and JACIE guidelines (6). The results of such transplants are reasonably well defined and compare favourably (or are superior to) results of non-transplant treatment approaches. Reporting of data to international transplant registries is considered as mandatory for EBMT members. Defining a transplant as the standard of care does not mean that it is necessarily the optimal therapy for a given patient in all clinical circumstances.

3.2.2. “Clinical option”

The next category is transplants classified as a “Clinical option”. This is the most difficult category. It encompasses many rare diseases and the paucity of data relating to transplant outcome, the variability in transplant techniques and the contribution of patient factors such as age and co-morbidity makes the assessment of indications for transplantation much more complex. Our current interpretation of existing data for indications in this category supports HSCT as a valuable option for individual patients after careful discussions of risks and benefits with the patient. However the value of HSCT for patients included in this category needs further evaluation. Furthermore, it is necessary to carefully consider the potential impact of various prognostic factors such as the nature of the donor, the stem cell source, and the conditioning regimens used, since outcome is likely to vary depending on these choices. We believe that transplants for indications under the “Clinical option” heading should be performed in a specialist centre with major experience with HSCT procedures, with an appropriate infrastructure as defined by EBMT guidelines and, optimally, should meet JACIE standards (6, 7). It is also important

that data from these procedures are reported to the international transplant registries in more detail (preferably on MED-B forms) that additional knowledge can be gained and used to further assess the value of HSCT in these indications.

3.3.3. “Developmental”

The third category is “Developmental” and indications have been classified in this category if there is little experience with this particular type of transplant and when additional research is needed to define the role of HSCT. These transplants should be done within the framework of a clinical protocol in which patients are offered the opportunity to undergo allogeneic or autologous HSCT in the context of a study that has been designed for individuals who satisfy defined diagnostic criteria. The protocol may be performed in a single institutional study or may reflect national or international multi-centre collaboration. Protocols for “Developmental” transplants will have been approved by local research ethics committees and must be performed according to current international standards. It is implied that the results of the study are intended for presentation to and/or publication for the medical community at large. Centres performing transplants under the category of “Developmental” should meet JACIE standards (5). The reporting of MED-B data to the international transplant registries is a prerequisite to allow further assessment of the value of HSCT in these indications.

3.3.4. “Generally not recommended”

Finally, we have also defined a “Generally not recommended” category. This category includes HSCT in early disease stages when results of conventional treatment do not normally justify the additional risk of transplant related mortality, or when the disease is so advanced that the chance of success is so small that the risk of the harvest procedure for the normal donor is difficult to justify. This grading may not apply to specific situations, e.g. where a syngeneic donor exists. This category also includes HSCT for a disease in a phase or status in which patients are conventionally not treated by HSCT. Therefore, there will be some overlap between “Generally not recommended” and “Developmental”. “Generally not recommended” does not exclude the possibility that centres with a focus on a certain disease can investigate HSCT in these situations. If a HSCT is performed for a “Generally not recommended” indication, the reporting of MED-B data is strongly recommended to allow further assessment of the value of HSCT in these indications.

4. Conclusion

It is beyond the scope of this Chapter to discuss the specific indications and their grading. Instead, we recommend consulting the latest published version of the

indications document and the accompanying disease specific Chapters in this handbook. However, based on these recommendations and on individualised risk assessments, a risk adapted strategy should be developed at diagnosis. Depending on the assessment, the transplant can be planned as initial treatment, as rescue therapy or be rejected. With better knowledge of the disease risks and the transplant risks, those algorithms will become more and more refined.

References

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