Indications for hematopoietic stem cell transplantation

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ABSTRACT

Transplantation of hematopoietic stem cells derived from bone marrow or peripheral blood has been used as a therapeutic procedure since the mid-seventies. In recent years, the number of transplants reported annually to the European Group for Blood and Marrow Transplantation (EBMT) Registry is approximately 23,500 including 38% of allogeneic and 62% of autologous procedures. In most developed countries, the incidence of hematopoietic cell transplantations reaches 400/10 million inhabitants per year and 220/10 million per year in Poland. Further advances require both increased funding and improved public health system as a whole. To recommend transplantation, it is necessary to compare the risk associated with the disease itself versus that of the transplantation procedure which depends on the stage of the disease, patient's age, time interval from diagnosis to transplantation, donor type (siblings or unrelated subjects), sex of the donor and individual features. According to the EBMT recommendations, the following categories of indications have been used: "standard procedure" category – S, "clinical option" – CO, indication of "developmental" character – D and "generally not recommended"– NR. The tabular presentation of indications is an approximation since approach to each patient should be individualized. Generally, the most-common indications for auto-transplant treatment are myeloma, malignant lymphoma and acute myeloblastic leukemia while the main indication for bone marrow allotransplantation is acute myeloblastic leukemia (33% of all allotransplantations), lymphoblastic leukemia, dysmyelopoietic syndrome, chronic myeloblastic leukemia refractory to tyrosine kinase inhibitors, then lymphoid malignancies and non-malignant disorders (bone marrow aplasia, severe immunodeficiencies, paroxysmal nocturnal hemoglobinuria, etc.).

Treatment with hematopoietic stem cell transplantation (HSCT) has been acknowledged as a method that cures certain diseases of the hematopoietic system. Its effectiveness is confirmed by an increasing number of procedures reported to the EBMT Registry which, in 2007, was approximately 23,536 including 14,524 of autologous and 9,012 of allogeneic transplants. Transplantation procedures are being more precisely described in Standard Operating Procedures, and the entities providing such treatment should obtain an appropriate accreditation and undergo control both at the national level (Ministry of Health in Poland) and international level (European Group for Blood and Marrow Transplantation [EBMT] and the Joint Accreditation Committee of the International Society for Cellular Therapy and the EBMT [JACIE] in Europe).

Transplantion of owne's hematopoietic cells (autologous transplant – AHCT) and hematopoietic stem cell transplantation from a donor (transplantation of allogeneic cells – alloHSCT) are part of the treatment process and have their place in the algorithm of the procedures provided for the treatment of certain types of leukemia, lymphoma and other less common diseases. Therefore, the indications for HSCT keep changing, which is the result of overall advances in medical practice. Factors of particular significance involve acknowledged benefits from transplantation in specific situations, better supportive treatment (anti-infectious drugs, blood preparations, treatment

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conditions) and the introduction of alternative medications in the therapy of some diseases.

Transplantations from unrelated donors are becoming more common alloHSCT owing to the development of registries for such donors, the system of their selection and cooperation between centers of a given country and international collaboration within the EBMT, the Bone Marrow Donors Worldwide, the National Marrow Donor Program, etc. Because of biological conditions, only one in four patients has a chance of having a donor from siblings, thus, the number of transplantations from the human leukocyte antigen-matched unrelated donors (MUD-HSCT) should be significantly higher than transplantations from siblings. In 2006, epidemiological data showed a similar incidence of alloHSCT from siblings and unrelated donors. Generally, the number of HSCTs performed around the world is increasing and the age limits are increasing for different indications. The curve of growth of autologous transplantations shows a transitory decrease in the nineties which has been caused by reduction in the number of procedures in patients with breast cancer. It was a result of a premature recognition and popularization of this treatment in oncology, mainly in the USA. This approach has been promptly verified. At present, an increase in the number of AHCTs using mainly peripheral blood-derived cells results from their increasing use in the treatment of myeloma, malignant lymphoma, less commonly in acute myeloid leukemia, and for experimental purposes, in autoimmune diseases. The curve of growth of alloHSCTs number also shows a slight short-term fall at the beginning of the first years of the 2000s which has been caused by the introduction of imatinib in the treatment of chronic myeloid leukemia and different tyrosine kinase inhibitors, which restricts indications for alloHSCT. At present, a further increase is observed, resulting mainly from indications for transplantation in leukemia and myelodysplastic syndromes, with a simultaneous increase of age limit. Factors which enhance this growth are the implementation of less toxic preparatory programs for transplantation (e.g. different conditioning of reduced intensity – RIC), advances in donor matching and better supportive treatment.

The rate of hematopoietic cell transplantations in certain highly developed countries was over 400/10 million inhabitants per year in 2000 and about 220/10 million per year in Poland in the last years. Further advancements require both increased funding and improved public health system a whole.. Transplantation is a component of the procedure algorithm where an appropriate management of the family doctor, the local hospital to which the patient will be admitted and the specialist center which provides the basic treatment are of significant importance. Without these, a considerable number of patients lose their chance of HSCT treatment.

Classification of indications for HSCT European centers of bone marrow transplantation belong to EBMT, and are obliged to report procedures and follow recommendations formulated by this organization. Rational indications for transplantation should be based on research results supported by their high quality. Such data can be obtained only in the case of common diseases and it is necessary to reiterate them along with the advances in medicine. Therefore, the indications are principally based on retrospective data analyses from registers and experts opinions. Studies performed by EBMT show that in less common situations, it is unlikely to conduct analyses sof a sufficient power of evidence, and, moreover, it is necessary to take into consideration the integrated observation of long-termside effects in long–living patients from different previously completed trials. Therefore, all studies should be considered as overall recommendations which must be individualized based on the patient's condition. Moreover, after the year 2000, the categories of indications have been more precisely formulated and the publishing of the tabular statement of indications was ceased for fear of their uncritical use. In this study, owing to the need of its concise presentation, a summary **TABLE** of indications has been shown. However, these indications should be interpreted as approximate recommendations with the previous reservations.

At present, the recommended by EBMT[1,4] categories of indications are the following:

1 "standard indication" category – S (standard of care, also the term "recommended" – R is used) which means that for a specific disorder and clinical situation the treatment with transplant was recognized as appropriately defined and found more beneficial than other treatments. However, it should be remembered that it might not be the best choice for every patient, thus, it is necessary to take into account general medical assessment. In such situations, the procedure can be performed in every accredited transplantation center with appropriate equipment and experience.

2 "clinical option" category – CO refers to a situation in which, according to the current knowledge, HSCT constitutes a good solution, holding promise for the patient that the benefits will outweigh the risk. Procedures within this category should be carried out according to specific protocols and reported so that they could facilitate the preparation of verified indications. Therefore, in the past years, these indications were defined as CRP (clinical research protocols). In every such a case the patient should be given information about his/her condition, benefits and risks of transplantation. The conscious consent and compliance of the patient are of extreme importance. The procedure should be performed in specialist centers with extensive experience.

3 "developmental" category – D refers to applications in which the experience is still insufficient so far to draw conclusions about the effectiveness

TABLE Indications for transplantation of hematopoietic stem cells in adults based on the EBMT recommendations

IllnessDisease	Risk group Stage of the disease	Allogeneic transplant		Autologous transplant
		From siblings	From unrelated donor	
Acute myeloblastic leukemia	Standard risk	CO	D	CO
	Standard risk: CR >1, progression	S	CO	CO
	Indirect risk: CR1* High risk in CR1 or every CR >1 and early phase of relapse	S	S	CO
	Lack of remission, advanced disease	D	NR	NR
Acute lymphoblastic leukemia	High risk and Ph + in CR1	S	CO	D
	Standard risk without molecular remission, every CR >1, early phase of relapse	S	CO	CO
	Stable relapse	D	NR	NR
Myelodysplastic syndromes	Indirect and high risk, in younger patients	S (RIC)	CO (RIC)	D
Chronic myeloid leukemia	Chronic phase when TKB are ineffective, or acceleration phase	S	S	D
	Blastic crisis	D	NR	NR
Myelo–proliferative syndrome	Osteomyelofibrosis, in younger people, in early stage of disease	CO	D	D
Non Hodgkin's lymphoma				
Aggressive NHL: from the peripheral cells TPTCL and diffused BDLBCL	CR1, risk indicator aaIPI 2–3			CO
All NHL aggressive recurrent	CR >1, PR	D	D	S
NHL of lower malignancy	CR1	NR	NR	D
	relapse; CR >1	CO	D	S
Hodgkin's lymphoma	CR1, higher risk		NR	D
	Relapsed disease, CR >1, PR	CO	CO/D	S
	Refractory form	D	D	D
Myeloma	CR1	NR	NR	S
	After progression CR >1, PR, high risk	CO	D	S
Chronic lymphocytic leukemia	High risk group, good biological condition	CO	CO	
	As consolidation			D
Solid neoplasm				
Breast cancer				D
From germ cells	Chemosensitive recurrence			S
	Resistant			NR
Ovarian carcinoma	Residual disease			D
	Resistant			NR
Glioma				D
Lung cancer				
Microcellular				D
Other forms				NR
Panmyelophthisis				
Serious aplastic anemia	Age <20 years	S	S	–
	Age >40 years	CO	CO	–
Autoimmunological diseases				
Systemic sclerosis				D
Multiple sclerosis				D
Visceral lupus erythematosus				D
Amyloidosis				D

* at risk of transplantation according to EBMT scale <2 points

Abbreviations: TKB – tyrosine kinase blockers, RIC – more often used as preparatory procedure for transplantation of reduced intensity, aaIPI – international risk indicator adjusted for age, CR >1 – consecutive remissions achieved after relapses, S – standard indication based on clinical trials, CO – justified indication, but requiring confirmation in clinical studies, CR1 – completely first remission, D – experimental use in clinical studies, NR – generally not recommended

and it is necessary to collect and creatively analyze observations regarding the course of treatment. It is recommended that treatment of that kind is carried out as part of clinical studies or at least with a detailed report in the centers which have JACIE accreditation (www.jacie.org) and are reported to the EBMT Registry providing detailed clinical data (B form, www.EBMT.org).

4 "generally not recommended" category – NR means the lack of indications for HSCT mainly for 2 reasons:

A when according to the current data, other treatment brings good results (e.g. patients with promyelocytic or lymphoblastic leukemia without risk factors in the first complete remission CR1

B when the disease is advanced and/or the patient's condition is too risky to perform transplantation (e.g. patients without remission, elderly patients with coexisting diseases, etc.). It should be mentioned that, in particular situations, the patients can be treated with transplantation at reference centers, preferably within clinical studies aimed at life saving and enhancing treatment progress.

Influence of different methods of preparation for transplantation (conditioning) on indications for transplantation The methods of preparation for transplantation are based on using a combination of medications (alkylating drugs, antimetabolites, natural or monoclonal antibodies) or total body irradiation in combination with medications. The basic treatment causes a total destruction of the recipient's bone marrow and is known as myeloablative therapy. Its benefit is a higher activity against the remains of cancer, easier implantation and, therefore, a lower probability of the relapse. A significant risk is, however, toxicity leading to more common infectious complications and damage to organs. It is the main cause of the so-called "age barrier" for transplantation, which, not so long ago, was about 40 years and could only be increased gradually due to progress in transplantation technology and supportive treatment.

The introduction of RIC had a decisive significance.[1,4] It was known as e.g. minitransplant, non-myeloablative transplant etc. From the biological point of view, RIC comprises preparations which do not completely excise the bone marrow (non-myeloablative) and also these, based on dose finding studies which have a minimum and difficult to avoid toxicity, but can be used in the majority of myeloablative patients. In case of RIC, early complications are rarer, but the role of removing the recipient's remains of the disease and the bone marrow is taken by the donor's lymphocytes. Therefore, such a transplantation requires a large number of transplantable cells and often splitting them off or providing the donor's lymphocytes (donor lymphocytes infusion). Moreover, a thorough management of the patient, preventing infections, observing chimerism and the remaining neoplastic disease are necessary measures which should be taken for several months. A number of studies show that transplantations after RIC are admittedly associated with lower mortality dependent on the transplant (transplant related mortality), but on the other hand, a higher probability of relapse (relapse incidence). However, at a result of it, the indications for transplantation can be extended to patients in a worse biological condition i.e. considerably older or with comorbidities. There have been reports on transplantations from siblings in people up to 75 years and from unrelated donors in recipients up to 70 years.[4]

Determination of transplantation risk in establishing indications When taking a decision, not only recommendations in respect of indication but also the risk associated with the procedure should be considered. The criteria for chronic myeloblastic leukemia known as the EBMT[1] criteria, which were suggested earlier and recently extended to different indications, are of significant help. They take into consideration the following issues, each of them with a value in points:

1 **advanced disease:** "early phase" (e.g. acute myeloblastic leukemia [AML] in CR1) – 0 points, "intermediary level (e.g. AML in CR2) – 1 point, "advanced illness" (e.g. AML resistant to treatment) – 2 points

2 **age:** <20 years old – 0 points, 20–40 years old – 1, >40 years old – 2 points

3 **period to transplantation:** <12 months/>12 months – 0 or 1 point

4 **transplant from siblings** – 0, from unrelated donor – 1 point

5 **sex of the donor:** female for male recipient – 1 point, other combinations – 0 points. In total, the risk is evaluated in the scale from 0 to maximum 7 points, which reflects statistically different probabilities of survival and, therefore, it has to be taken into consideration at qualification. Recently, it has been recommended to add one point for a bad general condition according to Karnowski's scale <80, the donor's age >50 years and for the situation when the donor and the recipient did not suffer from cytomegalovirus infection before. However, 1 point is subtracted for syngenic transplantations, that is from the monozygotic twin and for unrelated donors showing 10 points of matched alleles.

Clinical characteristics of indications For a general orientation, the indications are shown in TABLE. taking into consideration the diagnosis, progress of the disease and transplantation type. As explained above, such a presentation might be helpful to gain an understanding of general rules, however, this cannot be the basis for the procedure qualification. The TABLE is based on earlier EBMT studies with adjustments resulting from changes in indications and terminology.

AML is distinguished by the rate of transplantations. In 2007, transplantations in patients

with this disease constituted 33% of 8289 allogenic transplants and 15.6% of all 20 517 transplants in newly recorded patients.[3] The recovery rate after HSCT is approximately 50% in adults and 70% in children. The procedure should be carried out very promptly, even without the phase of consolidation in patients with high and moderate risk defined on the basis of cytogenetic and molecular examinations. Allotransplantation is effective even with the incomplete remission which results from strong graft versus leukemia (GVL) mechanism. When there is no donor among siblings and in patients at a higher risk and young individuals, unrelated donor transplantation is recommended, however, in the elderly with RIC conditioning. The autotransplantation proves also effectivees an option for patients without donor. AlloHSCT is effective in MDS when the treatment is intiated early. Since they are elderly patients, the transplants with RIC are used.

In high-risk acute limphoblastic leukemia (ALL), alloHSCT after consolidation is the best option, particularly if there is a family donor (long-term survival >60%). In case of Ph chromosome-positive ALL, tyrosine kinase blockers (TKB) are used in therapy. In ALL, the GVL mechanism is weaker, therefore, in unrelated donor transplantation, the risk associated with the treatment is not balanced enough with a low relapse rate, on the other hand the autoHSCT is associated with a very low incidence of early complications, but the relapse rate is high; the recovery rate in adults in such clinical settings is estimated at 40%.

So far, in chronic alloHSCT myeloid leukemia this is the only method that results in recovery of about 80% of patients if the procedure is performed in the chronic phase and within a year from the diagnosis. Howver, the introduction of TKB, such as imatinib, dasatinib, nilotinib that are easy in use and highly effective caused that HSCT treatment became a second choice which was taken into consideration in patients with resistance to or intolerance of TKB. The TKB treatment must be continued for the whole life but adverse effects of the treatment have not been well clarified yet, therefore, it is necessary to reiterate the estimation of indications for HSCT in very young subjects in the early period of TKB treatment.

In malignant lymphomas, autoHSCT is recommended as a standard procedure in recurrences with sensitivity to treatment. They are most often used in subsequent remissions after relapse. Treatment in the first remission is considered in patients with high risk factors and is included in the concept of the CO or D class indications. In resistant cases, particularly when bone marrow was infected, alloHSCT treatment is justified.

At present, the largest number of autoHSCTs is performed in myeloma, in which it was recognized as a component of consolidation treatment after remission. It can be used as two consecutive procedures called tandem autoHSCT. In young people, allotransplantation should be considered as the only option giving a chance of recovery.

Among non-neoplastic diseases, alloHSCT has an established position in severe bone marrow aplasia and in different inborn hematological disorders. The HSCT in autoimmune diseases has been used in clinical studies.

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