HAEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CHILDREN IN BELGIUM

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ABSTRACT

Haematopoietic stem cell transplantation has become a well-established therapy for many severe congenital or acquired disorders of the haematopoietic system. Contrarily to most European countries, there is no Registry of Haematopoietic Stem Cell Transplantation in Belgium. A retrospective study revealed that results of Belgian paediatric transplantations were similar to results of the European for Blood Marrow Transplantation (EBMT) group.

In the field of Haematopoietic Stem Cell Transplantation, an accreditation of transplant centres should been required to be allowed to perform transplantations. The Joint Accreditation Committee-ISCT & EBMT (JACIE) is a non-profit body established in 1998 for the purposes of assessment and accreditation in the field of haematopoietic stem cell transplantation

In Belgium, it is likely that in the future the centre density (the highest of Europe) will decline. On request of JACIE, a centre should be accredited for allogeneic transplantation only if it performs > 10 allografts per year. For the pediatric activity, an average of about 20-25 allografts per year were performed for children (<18 years) in the last past five years.

Introduction

Haematopoietic stem cell transplantation (SCT) has become a well-established therapy for many severe congenital or acquired disorders of the haematopoietic system. Contrarily to most European countries, there is no Registry of Haematopoietic Stem Cell Transplantation in Belgium. A retrospective study (2) revealed that results of Belgian paediatric transplantations were similar to results of the European for Blood Marrow Transplantation (EBMT) group (www.ebmt.org).

EBMT is a non-profit organisation established in 1974 in order to allow scientists and physicians involved in clinical bone marrow transplantation to share their experience and develop cooperative studies. In 1996, the “EBMT Working Party Paediatric Diseases” was created.

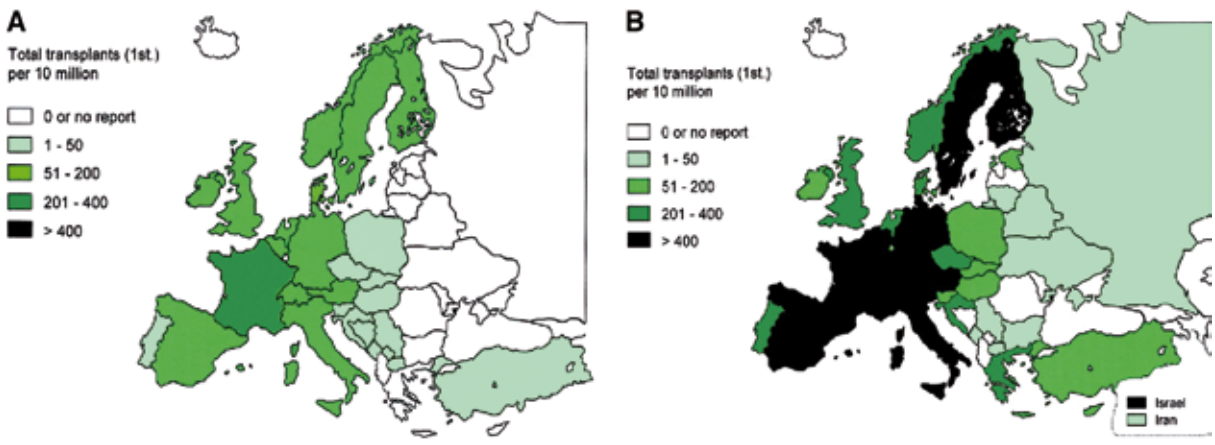

Figure 1: Haematopoietic Stem Cell Transplantation rate in Europe in 1990 (A) and in 2000 (B). (4)

Activity in Europe: EBMT

In 2002, 586 centres in 39 European countries carried out 20,207 transplantations (30% allogenic and 70% autologous). The highest team density in Europe (defined by the number of centres per 10 millions inhabitants) is found in Belgium (18.4 centres for 10 millions inhabitants). The lowest density centre is found in England (8.8) and in Holland (8.7).

The source of stem cells varied in time. In 1990, bone marrow cells were the principal source of cells. Ten years later, 80% of grafts originated from peripheral blood stem cells. The first cord blood transplantation was performed in 1989. In 2002, 162 cord blood transplantations were performed in Europe. The transplantation rate (defined by the number of transplants by 10 millions inhabitants) is variable from one country to another (Figure 1). In Belgium, it is high (more than 400 transplants by 10 million inhabitants) (4) Figure 2 shows the evolution of transplantation in Europe from 1990 to 2000.

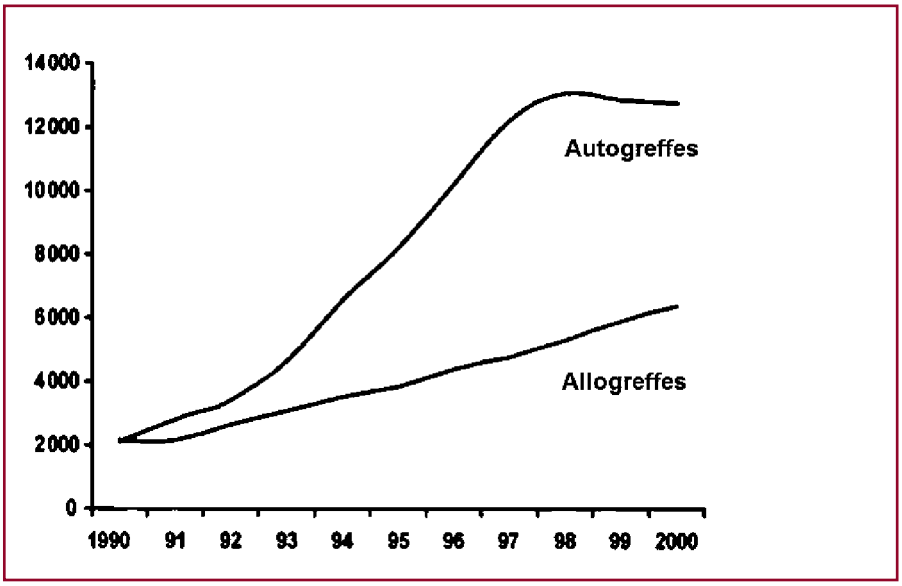

Figure 2: Number of transplants (autografts and allografts) per year in Europe from 1990 to 2000. (3)

Haematopoietic stem cell transplantation in Belgium

The Marrow Donor Program Belgium was created to recruit and facilitate transplantations from Belgian and foreign donors.

Today, a patient search for a matching marrow or blood cell donor can include more than 6 millions volunteer donors on the National Marrow Donor Registry (NMDP; http://www.marrow.org/ABOUT/Cord_Blood/NMDP_Center_for_Cord_Blood) in the United States, the largest donor registry in the world. An additional 4 millions volunteer donors are available in other international registries. The Registry Networks extend worldwide, with donor centres, transplant centres and registries having cooperative agreements.

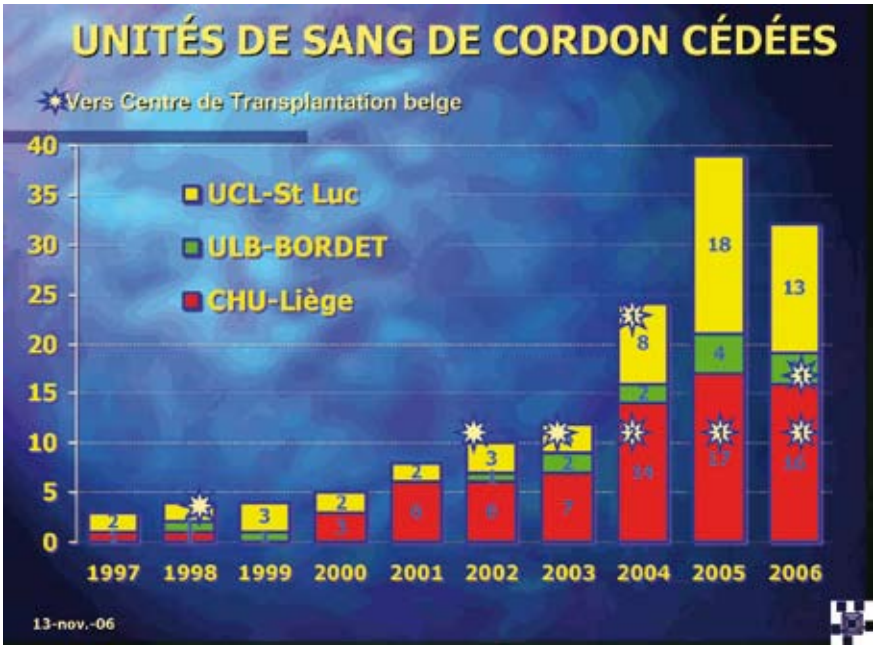

Figure 3 : Number of cord blood units from the Belgian cord Blood Bank used for transplantation from 1996 to 2006 (www.chuliege.be : Laboratory of Cellular and Gene Therapy-Cord Blood Bank)

Cord blood transplantation has the potential to significantly increase the opportunity for transplant for seriously ill patients, especially those from ethnically diverse communities. Through the international network of cord blood banks Netcord, more than 150,000 cord blood units are listed in the world.

The «Belgium Cord Blood Bank» was created in 1993. Three cord blood banks were created with the funds of "Le Fonds National de Recherche Scientifique" (FNRS) and the yearly "Télévie" fund raising project. They are based at the Catholic University of Louvain (UCL), the Free University of Brussels (ULB) and the University of Liege (ULg). More than 5.000 cord blood units are stored in these banks. The number of units used for transplantation increases constantly (Figure 3).

Other cord blood banks have also been created at the Catholic University of Leuven (KUL) and the University of Ghent (RUG).

Paediatric activity in Europe : EBMT

Paediatric transplants (children < 18 years) represent 18 % of all the transplant activity during the period from 1970 to 2003 (1). Paediatric transplants were performed in 395 centres in 28 European countries. Only 25% of the centres performed exclusively paediatric transplants. But in the last years, the proportion of centres treating only children increased, with a figure of 40% (n=89) in 2002. From 1970 to 2000, the vast majority of paediatric transplantations were performed in 5 countries: France (n=7,076), Italy (n=5,429), UK (n=3,622), Germany (n=2,188) and Spain (n=2,034). Belgium registered 513 paediatric transplants (allografts: 315, autografts: 198). Contrary to adults, allogeneic transplants represent the vast majority of paediatric activity. The more frequent indications for paediatric transplantation were acute lymphoblastic leukaemia (ALL) (n=8,340, 76 % allogeneic), solid tumour (n=7,956, 97 % autologous), non malignant disease (n= 7,424, 98 % allogeneic), acute myeloid leukaemia (AML) (n=4,788, 67 % allogeneic), lymphoma (n=2,480 , 80 % autologous), chronic myeloid leukaemia (CML) (n=1,183, 96% allogeneic) and myelodysplastic syndrome (MDS) (n=697, 96 % allogeneic).

Since 1996, the number of children treated with an allograft for ALL, AML or CML is stable. But more allografts are performed for lymphoma and MDS. The number of autografts for ALL and AML has dropped considerably. In contrast, the number of autografts for solid tumour is increasing.

In 2005, the EBMT defined the indications for haematopoietic stem cell transplants based on the disease and the donor (7). (Table 1)

DISEASE	STATUS OF THE DISEASE	ALLO		AUTO
		FAMILIAL	UNRELATED	
Acute myeloid leukemia	CR1 (low risk) CR1 (high risk) CR1(very high risk) CR2	NR S S S	NR CO S S	NR S NR S
Acute lymphoblastic leukemia	CR1 (low risk) CR1 (high risk) CR2 >CR2	NR S S S	NR CO S S	NR NR CO CO
Chronic myeloid leukemia	Chronic phase Advanced phase	S S	S S	D NR
Myelodysplastic syndrome		S	S	NR
Immunodeficiency		S	S	NA
Non – Hodgkin's lymphoma	CR1 (low risk) CR1 (high risk) CR2	NR CO S	NR CO S	NR CO CO
Hodgkin's disease	CR1 First relapse, CR 2	NR CO	NR D	NR S
Thalassemia major		S	CO	NA
Sickle cell disease		S	CO	NA
Severe aplastic anemia		S	S	NA
Fanconi anemia		S	S	NA
Blackfan-Diamond anemia		S	CO	NA
Solid tumour	Germ cell tumour Ewing sarcoma Soft tissue sarcoma Neuroblastoma Wilms tumor Osteosarcoma Brain tumour	NR D D CO NR NR NR	NR NR D NR NR NR NR	CO S CO S D CO
Auto-immune disease		NR	NR	CO

CR1: first complete remission, CR2: second complete remission, CR3: third complete remission, S : standard of care, CO : clinical option, can be carried out after careful assessment of risks and benefits, D : developmental, further trials are needed, NR: non recommended indications, NA : not applicable.

Paediatric transplantation activity in Belgium

Between 1970 and 2000, 513 children (<18 years) were registered at the EBMT for Belgium. This included 315 allotransplants and 198 autotransplants. However, these numbers are not complete...

A retrospective study was thus conducted on the 595 paediatric transplants performed between 1988 and 1999 in Belgium. Paediatric transplants in Belgium represented 13.5 % of the Belgian activity (in the EBMT paediatric activity is 18%). The number of paediatric transplants per year is relatively stable (Figure 4).

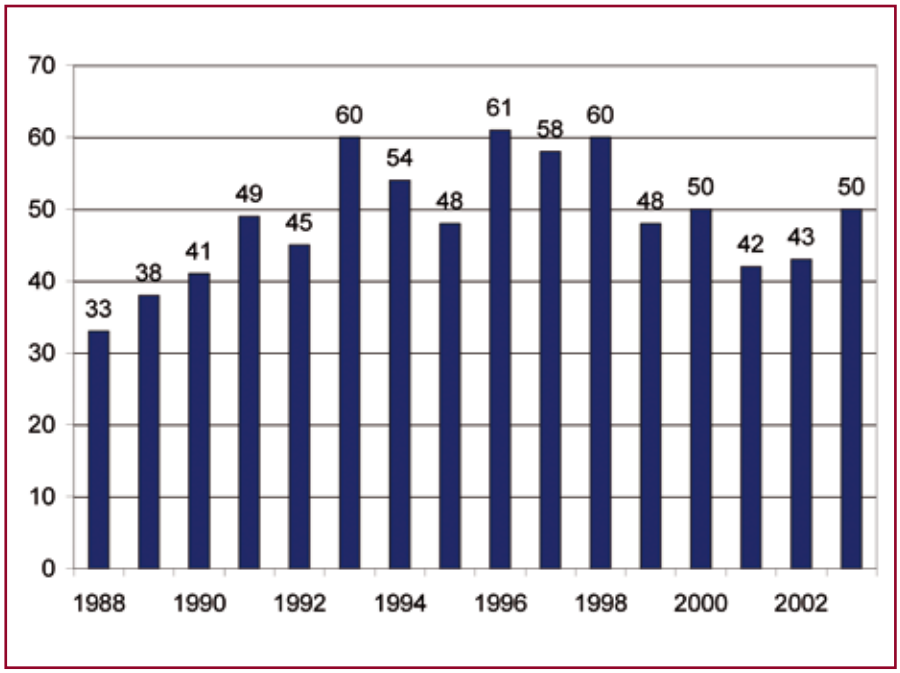

Figure 4: Number of paediatric transplants in Belgium between 1988 and 2003

A difference was noted in the proportion of paediatric centres in the EBMT (38.5%) and in Belgium (12.5%). Among the 24 Belgian transplant centres, paediatric transplants were performed in 6 centres. Two centres performed only paediatric transplants (UCL and HUDERF) and six centres performed only autografts. Contrary to the adults, the majority of transplantations were allogeneic (64%), with 27% performed with an unrelated donor, a proportion similar that reported by the EBMT (60% allogeneic). Indications for transplantation in children in Belgium are the same as in the EBMT, except that more transplants are performed for sickle cell anemia and fewer autografts for solid tumour in Belgium. The majority of paediatric transplants are performed for leukaemia and myelodysplasic syndromes (46% of all paediatric transplants in Belgium).

The Event-Free Survival (EFS) for the whole group of paediatric transplants is 57% at 1 year and 48% at 5 years. There is no statistically significant difference between results of allografts and autografts but they are performed for different indications. In general, these results are comparable with the

results from the EBMT and the IBMTR (International Bone Marrow Transplant Registry) (htpp://www.ibmtr.org). Like in other registries, there is no difference between allografts performed with bone marrow or peripheral blood stem cells (PBSC), but more chronic graft-versus-host disease (CGVHD) is seen when the graft is from PBSC. (9) During the period covered by our retrospective study, results of unrelated donor transplants were worse in Belgium. But this cohort is limited in number and closed in 1999. In the last 5 years, progress has been made in unrelated transplants, with results becoming comparable with those of familial transplantation. (5,6) Indeed the year of transplantation has a significant impact on the results for unrelated transplants. (8)

Contrarily to other European countries, in Belgium, there is not yet a "Pediatric Oncology Program". In the field of Haematopoietic Stem Cell Transplantation, an accreditation of transplant centres should been required to be allowed to perform transplantations.

The Joint Accreditation Committee-ISCT & EBMT (JACIE) is a non-profit body established in 1998 for the purposes of assessment and accreditation in the field of haematopoietic stem cell transplantation. The Committee was founded by the European Group for Blood and Marrow Transplantation (EBMT) and the International Society for Cellular Therapy (http://www.celltherapysociety.org), the two leading scientific organisations involved with SCT transplantation in Europe. JACIE's primary aim is to promote high quality patient care and laboratory performance in haematopoietic stem cell collection, processing and transplantation centres through an internationally recognised system of accreditation. JACIE (http://www.jacie.org), in collaboration with the Foundation for the Accreditation of Cellular Therapy (http://www.factwebsite.org) in the USA, has established standards in SC, encourages health institutions and facilities performing SCT to voluntarily meet these standards, and conducts inspections and acknowledges compliance with the standards by issuing Certificates of Accreditation.

In Belgium, it is likely that in the future the centre density (the highest of Europe) will decline. On request of JACIE, a centre should be accredited for allogeneic transplantation only if it performs > 10 allografts per year. For the pediatric activity, an average of about 20-25 allografts per year were performed for children (<18 years) in the last past five years.

Currently, funds for a Belgian Registry of Haematopoietic Stem Cell Transplantation under the umbrella of the Belgian Haematological Society (BHS) are in discussion at the Public Health levels.

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