AUTOLOGOUS AND ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDREN WITH LYMPHOMA

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Childhood lymphomas constitute the third most common group of malignancies in the population aged from 0 to 17 years [1]. It accounts for approximately 14% of all newly diagnosed childhood cancers. Among all pediatric lymphomas, 60% of children are diagnosed as having non-Hodgkin's lymphoma (NHL), and 40% Hodgkin's disease (HD). However, pediatric NHLs account for only about 3% of all NHLs in Western countries. In Poland, more than 150 new cases of childhood lymphomas are registered each year (table 1). In contrast to other European countries in Poland, an almost equal distribution of NHL and HD is has been observed in recent 5 years [2].

Table 1. New Cases of childhood lymphomas in Poland

	1995	1996	1997	1998
Total	122	161	151	155
NHL	68	79	72	89
HD	54	79	72	66

The histological spectrum of childhood NHL is considerably narrower than that of adult NHL. The most common type in adults is the low grade, relatively indolent NHL such as follicular lymphoma, this histology beeng exceedingly rare in children. Pediatric malignant lymphomas are generally diffuse aggressive with a propensity for widespread dissemination. Half of them are formed with small noncleaved cells (Burkitt's or Burkitt's like), 30% are lymphoblastic and 20% are large cell anaplastic lymphomas (LCAL) – [1].

In recent years, a marked improvement in event-free survival (EFS) rates has been achieved due to intensification of conventional chemotherapy and efficient supportive care. In most reports, the EFS for nonB-NHL stage I/II ranges from 80% to 100%, and stage III/IV from 65% to 80%. For B-NH these values are 90%-100% and 75%-85%, respectively. The EFS for LCAL are lower: 50-70%. In Poland, these rates are still not as high as in other developed countries. The reason is that more pediatric patients are diagnosed at advanced stages of disease, i.e. at stage III and IV, and only few at stage I and II. For example, 89% of patients with childhood NB-NHL and 83% with B-NHL are diagnosed at stage III+IV [3]. Since in these patients conventional chemotherapy is not as efficient as in those at stage I+II, they can benefit from megachemotherapy, followed by autologous hematopoietic stem cell transplantation.

The first description of high-dose therapy and autologous bone marrow transplantation were recorded as early as 1957 for patients with non-Hodgkin's lymphoma [4]. However, the authors were not able to show any evidence of curative potential of the method and this approach was not widely endorsed at that time. In 1978, a clinical study of Appelbaum and others [5] suggested for the first time that patients with refractory lymphoma could sometimes experience a long-term relapse-free survival after high-dose chemotherapy, followed by bone marrow transplantation. These results caused a renewed interest in HDT + BMT, generating studies designed to determine which lymphoma patients were the best candidates for the procedure. Until 1994, the gold standard for autograft was bone marrow. After 1994, the Autologous Blood and Marrow Transplant Registry for North America (ABMTR), the International Bone Marrow Transplant Registry (IBMTR) and the European Group for Blood and Marrow Transplantation (EBMT) reported that more autologous peripheral blood stem cell transplantations than autologous bone marrow transplantations were performed in patients with lymphoma (figure 1 and 2). High-dose chemotherapy followed by hematopietic stem cell transplantation, both autologous and

allogeneic, becomes an accepted treatment for NHL patients who failed or relapsed after conventional therapies. At the same time, the autologous blood was used with increased frequency as a source of haematopoietic rescue following high-dose chemotherapy. By February,1998, a total of more than 10.000 autologous transplants were registered in NHL, and almost 5000 in HD, with much fewer allogeneic transplantations [6] (table 2 and 3).

It should be stressed however, that most studies were based in adult patients, and only 4% of transplants were performed in children below 17 years of age. The majority of patients with NHL were transplanted while at first complete remission, partial remission or at second remission. Hodgkin's disease patients were transplanted at a time of a sensitive relapse or after second remission (table 4).

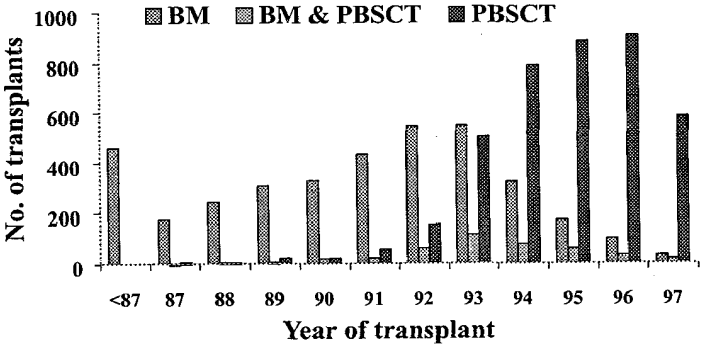

Fig. 1. NHL: Type of transplant (Lymphoma Working Party, EBMT 1998)

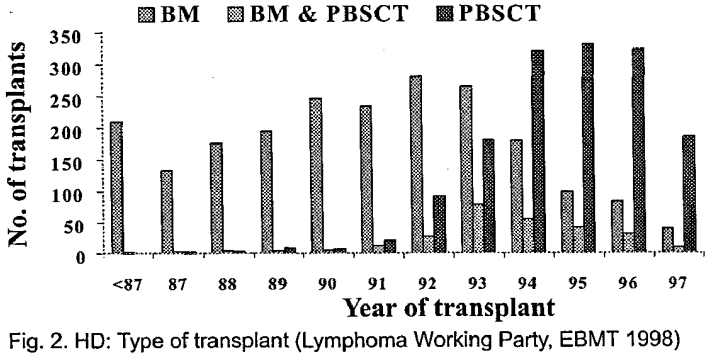

Fig. 2. HD: Type of transplant (Lymphoma Working Party, EBMT 1998)

Table 2. EBMT Registrations by February, 1998.

Disease	Transplant type		
	Auto	Allo	Cord blood
Ac. leukemia	9020	13214	63
CML	1007	7039	13
CLL	163	165	-
NHL	10155	1108	4
Hodgkin's	4808	163	-
M. Myeloma	4785	765	-
Solid tumours	9945	125	8
MDS / MPS	137	1423	8
SAA	4	2613	21
Imm. deficiencies	2	496	2
Inborn errors	1	1532	17
TOTAL	40027	28643	136

Table 3. Transplants in pts with NHL and HD performed in Europe in 1998 (Gratwohl A., Baldomero H. for EBMT, 1999)

	DONOR SOURCE													
	ALLOGENEIC								AUTOLOGUS			TOTAL		
	FAMILY						UNRE-LATED							
	HLA-id		Non-id		Twin									
	BM	PB	BM	PB	BM	PB	BM	PB	BM	PB	BM+PB	Allo	Auto	Total
NHL	105	98	3	13	5	8	18	3	140	3154	87	253	3381	3634
HD	6	14	–	3	–	1	5	–	100	947	40	29	1087	1116

Table 4. Demographic data (Lyphoma Working Party, EBMT 1998).

Status at transplant	HD (%)	NHL (%)
CR1	312 (7.8)	2493 (28.2)
CR2	714 (17.9)	1598 (18.1)
≥ CR3	260 (6.5)	299 (3.4)
(VG) PR	705 (17.6)	2057 (23.2)
sensitive relapse	801 (20.0)	1191 (13.5)
untested relapse	346 (8.7)	250 (2.8)
resistant relapse	427 (10.7)	437 (4.9)
primary refractory	431 (10.8)	524 (5.9)
TOTAL	**3996**	**8849**

High-dose therapy followed by haematopoietic stem cell transplantation produces better results when compared with conventional chemotherapy. Early non-randomized trials showed that the probability of a long-term disease-free survival was 20 – 50% in patients with relapsed aggressive NHL compariel with 5 – 10% in similar patients receiving conventional salvage therapy [7, 8, 9, 10, 11]. A multicentre randomized trial conducted by Philip and co-workers [12] included patients with chemotherapy-sensitive, relapsed, intermediate/high-grade NHL after 2 cycles of DHAP. The patients were randomized to receive either additional 4 cycles of DHAP or high-dose therapy followed by autologous BMT. Event-free survival at 5 years for the transplant arm was 46% vs. 12% in patients receiving salvage therapy. Overall survival rates showed also differences of 53% vs. 32%, respectively. The data collected by the Lymphoma Working Party indicate similar rates for transplanted patients (figure 3 and 4).

The efficacy of high-dose therapy + HSCT in patients with either primary refractory or relapsed lymphoma that is chemotherapy resistant still remains controversial. ABMTR analysis evaluated 221 patients who had never achieved CR prior to undergoing high dose chemotherapy and autologous transplantation [13]. The progression-free survival at 3 years was 32%, and overall survival was 40%, but for

those with resistant disease the overall survival was 19% vs.48% for patients with sensitive disease. The only prognostic variable found to be significant in this study was sensitivity to prior chemotherapy. For chemoresistant patients with EFS of 10 – 20%, what can be probably most beneficial is early identification and use of modulating agents or anti-lymphoma antibodies such as IDEC C2B8 or B1.

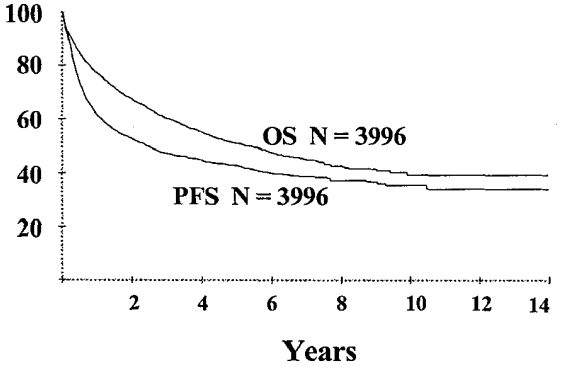

Fig. 3. Hodgkin's disease (Lymphoma Working Party, EBMT 1998).

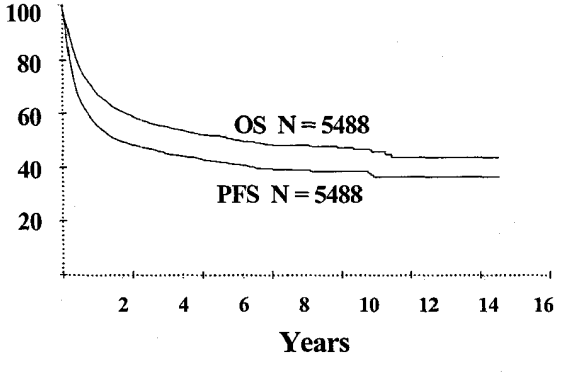

Fig. 4. Intermediate and high grade lymphoma (Lymphoma Working Party, EBMT 1998)

Polish BMT centers have transplanted 26 children with NHL (December 1999).
AutoHSCT was performed in 14 children with B-NHL, 6 LCAL and 6 with T-NHL. The majority of patients were transplanted during 1999, and the observation time after transplants is too short, for us to came to any definitive conclusions as to the results of this therapy.

Many factors lane influenced the interpretation of the results. The patients' populations in and between published studies are laterogenous. Almost all studies are have been related to adults including patients with varying proportions of different histologies and prognostic factors. Several studies have reported on series of partial responders and non-responders mixed together. Finally, front-line treatment of aggressive NHL has varied from study to study. Comparison of all these results is difficult and, sometimes, even impossible, which results in several controversies.

The major areas of controversy are:

1. Selection of high-risk patients for transplantation in the first remission,
2. An optimal source of stem cells,
3. Optimization of mobilization procedures,
4. An optimal transplant regimen,
5. The value of purging or positive selection,
6. Pre- or post-transplant immunotherapy

Transplantation of haemopoietic stem cells is recommended for relapsed, chemosensitive patients with aggressive forms of NHL. Also, approximately 10 – 15% of patients with chemotherapy-resistant, relapsed aggressive NHL can benefit from this strategy [14]. The third group which can benefit from HSCT in 40 –70% of cases are patients with residual lymphoma following standard treatment [15, 16, 17].

The currently adopted recommendations for HSCT in childhood NHL and HD are as follows:

- High risk NB-NHL, T-NHL, LCAL - in CR1,
- NB-NHL regardless risk factors - in CR2, early relapse or partial remission,
- B-NHL, T-NHL – at relapse,
- Hodgkin's disease – at relapse or in CR2

The discussion on the optimal source of stem has revealed the superiority of mobilized peripheral blood progenitors over bone marrow with respect to engraftment rates of neutrophiles and platelets. Most advantages of PBSCT lie in faster engraftment, lower costs and shorter hospitalization and no evidence of inferiority with respect to outcome.

Prospective randomized trials comparing HLA-matched related vs. autologous haematopoietic stem cell sources have not yet been published. Several nonrandomized studies have shown that alloBMT reduces the risk of lymphomatous relapse lown to 18 – 24% vs. 38 – 69% with autoBMT. However, the lower relapse risk has been offset by higher transplant related mortality and serious morbidity, thus no overall statistically significant benefit in EFS or overall survival could be proved. Except in unusual circumstances, an unrelated allogeneic or partially matched related source of stem cell for children with lymphoma is not recommended.

The optimum mobilizing strategy should assure that apheresis product contains:

- A maximum number of stem/progenitor cells,
- A minimum number of autologous tumor cells,
- A maximum number of cytotoxic cells,
- A sufficient number of cells necessary for recovery of immune function following transplantation.

Currently, myelosuppressive chemotherapy followed by haematopoietic growth factors is used clinically to mobilize progenitor cells into circulation for more efficient collection and to provide rapid haematopoietic recovery after transplant [18, 19]. The benefits of growth factor plus chemotherapy for mobilization include vigorous mobilization and, in some instances, the ability to use a cycle of already scheduled chemotherapy along with growth factor. Not all patients exhibit haematopoietic progenitor cell mobilization after administration of myelosuppressive chemotherapy and growth factors: in some patients poor or no response can be observed. Donor characteristics that have been associated with poor or no response to mobilization therapies include prior treatment with several cycles of chemotherapy or radiation therapy and the presence of marrow metastases [20, 21].On the other hand, to avoid some occult tumour cells in autograft product the mobilization procedure should not be started before the induction phase of the front-line therapy is finished.

Table 5. BEAM Proctol

	-7	-6	-5	-4	-3	-2	0
BCNU 300mg/m	X						
VP16 200mg/m		X	X	X	X		
Ara-C 200mg/m / 12 hrs		XX	XX	XX	XX		
Melfalan (Alkeran) 140mg/m						X	
ABMT/PBSCT							X

The optimal conditioning regimen for transplantation in NHL is unknown and no randomized trials have been performed. The most commonly employed regimes are the TBI-containing (CY/TBI, VP-16/CY/TBI), and the chemotherapy only regimens (CBV, BEAM, BEAC). In children, the most useful regime seems to be BEAM (tab.5). An interesting approach to conditioning regimens for lymphoma recently been presented in substitution of targeted radiotherapy by using radiolabeled antibodies to replace TBI [22]. The early phase II trial evaluated 19 patients treated with ^{131}I-anti-CD20(B1) followed by haematopoietic stem cell infusion. As a result, 50% of patients achieved complete remission. Ongoing studies combine radioimmunotherapy with other standard transplant regimens such as BEAC.

The purging of bone marrow and the apheresis product, or positive selection of CD34 positive progenitor cells in some HSCT protocols is performed in some transplantation protocols. Significance of the tumour cell contamination in bone marrow or apheresis product is unclear. Only a small number of tumour cells are clonogenic, and the host immune system may be able to eradicate at least some of the contaminating cells. There is also evidence that almost all relapses occur at sites of prior disease indicating that the relapse is most likely due to failure of the conditioning regimen to eradicate the bulk disease rather than haematogenous spread of infused clonogenic lymphoma cells. However, in the clinical trial conducted at Dana Farber Cancer Center, patients with low-grade NHL were serially monitored for expression of the t(14;18) before and after marrow purging with anti-CD20 antibodies and complement [23]. Disease free survival of patients succesfully purged to t(14;18) negativity was 90% compared with DFS of 25% for patients in which translocation was detected in the transplanted marrow.

The feasibility of the use of positive selection techniques for CD34+ cells has been documented. Unfortunately, large or randomized trials in lymphoma have not been performed to document the effects on engraftment, relapse rates, EFS, OS and immunologic reconstitution.

New possibilities in the treatment of NHL have arisen with increased knowledge of the biology of lymphoma cells. The most promising is immunotherapy by post-transplant administration of interleukine 2, alfa interferon, anti-CD19 immunotoxin, tumour reactive T-lymphocytes to eradicate minimal residual disease after transplantation. Addition of anti-

CD20 antibodies, both unmodified and radiolabeled, to the transplant regiment may also improve treatment results. Vaccination of patients with tumour specific idiotype vaccines or mini-allogeneic transplants are worthy of interest in future trials.

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