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The results of allogeneic transplants in patients with malignant lymphoma-a retrospective analysis of data from the Czech National Registry

V. VALKOVA[1*], K. BENESOVA[5], A. VITEK[1], E. FABER[2], J. MAYER[3], P. ZAK[4], M. TRNENY[5]

[1]Institute of Haematology and Blood Transfusion, Prague 2, Czech Republic, e-mail: veronika.valkova@uhkt.cz [2] Clinic of Haemato-Oncology, University Hospital Olomouc ,[3] University Hospital and Clinic of Haemato-Oncology, Brno, [4] 2nd Clinic of Internal Medicine, Department of Clinical Haematology, Charles University Medical Faculty in Prague and Hradec Králové, [5] Czech National Registry of Haematopoeitic Stem Cell Transplantation, Charles University Hospital, Prague

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We processed data of 79 patients (pts) with malignant lymphoma from the National Registry of haematopoietic stem cell transplants conducted between 1997 and 2006. The haematopoietic stem cell donor in 48 pts was an HLA matched relative, and in 30 pts an unrelated volunteer. Sixty (77%) pts were transplanted with reduced intensity conditioning (RIC), eleven (23%) pts with myeloablative conditioning (MC). Acute graft-versus-host disease (aGVHD) was recorded in 26 (33%) pts. Chronic GVHD was diagnosed in 19 (36%) of the 53 assessable pts. Transplant-related mortality (TRM) in the first 100 days, 1 year and 3 years for the whole group was 26%, 33% and 33%. Twenty (26%) of the pts relapsed. During the median follow-up of 26 months the overall survival (OS) was 44%, the progression free survival (PFS) was 54% and cumulative incidence of relapse was 45%. Pts with chemoresistant disease had significantly worse results (OS at 3 years 22% vs. 56%, p=0.002). We did not find any correlation between the incidence of GVHD and the frequency of relapse. Similarly, we did not observe any difference in survival between patients following MC vs. RIC. Survival of pts transplanted from related donors did not differ statistically from unrelated donors.

Keywords: Lymphoma, allogeneic, transplantation, GVHD

New therapeutic modalities, including high-dose chemotherapy and autologous haematopoietic stem cell transplantation (ASCT) and treatment with monoclonal antibodies, currently represent a curative approach in a number of patients with malignant lymphoproliferative disease. Autologous transplantation is considered to be a standard method of choice in relapsing lymphoma [1]. Nonetheless, there exists a group of patients (either those at high risk due to biological factors of the disease, or due to the unfavourable disease course with repeated relapses) in whom standard therapeutic modalities (including ASCT) fail. For this group of patients, allogeneic transplantation (allo-SCT) represents some hope, especially in the form of the immunological graft versus leukaemia/lymphoma (GVL) effect. The first observation regarding the anti-tumor effect of allogeneic immuno-competent cells dates from 1956 and relates to animal models [2]. The period between 1970-1980 saw further proof of the graft-versus-leukaemia effect following allogeneic transplants in patients with acute leukaemia. A lower incidence of relapse was noted following allogeneic transplants compared to syngennic transplants [3]. A lower incidence of relapse was recorded also in patients who developed graft-versus-host disease – GVHD [4, 5] and, in contrast, a higher incidence of relapse was noted following so-called T-cell depletion of the donor graft [6]. In the 1990s, these observations were confirmed in a large analysis of data from the International Bone Marrow Transplantation Registry (IBMTR) [7].

Standard allo-SCT is still associated with high peri-transplant mortality (TRM), 20-60% according to data in literature [8, 9, 10]. This is why, in the past few years, so-called non-myeloablative transplants (or transplants using reduced intensity conditioning, RIC–alloSCT) have come to the fore. The reason for searching for such less toxic approaches is the frequently older age of the patients who often suffer from concomitant diseases that represent a limitation for myeloablative transplants.

According to recent works, it appears that it has been possible significantly to reduce TRM in RIC allo-SCT, especially in the group of patients with low grade lymphoproliferation.

* Corresponding author

We present here the analysis of data relating to allogeneic transplantation in lymphomas from four centres in the Czech Republic in the period from 1997 to 2006.

Patients and methods

The data regarding the haematopoietic stem cell transplants (SCT) were acquired from the central computer database of the European Group for Bone Marrow Transplantation (EBMT) PROMISE in London. Data relating to SCT performed in transplant centres in Prague, Brno, Hradec Králové and Olomouc was collected by them Czech National SCT Registry in Prague. These data related to the patient (age, sex, date of diagnosis, disease phase at the time of SCT), the transplant itself (date of SCT, type of conditioning, type of graft), the donor (type of donor, sex), complications following SCT (incidence of acute and chronic graft-versus-host reaction and its extent), and patient follow-up (date and type of relapse, date and cause of death, date of last follow-up visit). Additionally, we included also data regarding the type of the transplant regimen and manner of T-cell depletion.

Definitions. Most of the histological diagnoses were reclassified in accordance with the WHO classification following re-examination by reference pathological institutions (second or more readings). In those cases, where it was not possible to re-ascertain the diagnosis in accordance with the WHO classification, the term lymphoma-unspecified was kept.

Chemosensitive disease was that, which responded to the last chemotherapy administered before transplant; partial remission (PR), unconfirmed complete remission (CRu) and complete remission (CR). Chemoresistant disease was that, which was primarily refractory or a refractory relapse before transplant [35].

Acute and chronic GVHD were evaluated according to the consensual criteria [11, 12]. Only those patients who survived 100 days after transplant were evaluable from the aspect of chronic GVHD. OS was defined as the period from the day of transplant until the day of death from any cause. PFS was defined as the period from transplant until relapse/progression or death from any cause. Any death associated with the transplant regardless of the status of the primary disease was evaluated as peri-transplant mortality [TRM].

Statistical analysis. Correlation analysis and analysis using the Mann-Whitney rank-sum test and the non-paired t-test were used to show the trends of numerical values during the follow-up period. Pearson's chi square test or the method of contingent tables using Fischer's exact test were used to show the trends of categorically variable values. Calculations according to Kaplan Meier were used to determine the probability of overall survival and disease free survival. The log-rank test was used to compare the statistical significance of the differences in the probability of survival between the individual groups of patients. Cox regression analysis of risks was used to determine the independent factors affecting the probability of patient survival. The GraphPad PRISM 4 was used for the statistical analysis. The tests were conducted at a level of significance of 0.05.

Results

Patient characteristics. We analysed a total of 78 patients with malignant lymphoma transplanted in the period from June 1997 and September 2007. These included 49 men and 29 women. These patients ranged in age from 19-64 years (median 45 years). Twenty-five patients were older than 50 and only 5 patients were older than 60. The following histological subtypes were included: 17x follicular lymphoma (FL), 18x Hodgkin's lymphoma (HL), 16xdiffuse large B-cell lymphoma (DLBCL), 9x mantle cell lymphoma (MCL), 8x peripheral T-cell lymphoma (PTL) and 10 unspecified lymphoma (others). Forty-one patients 41 (53%) were relapsed lymphomas following autologous transplantation. Forty-eight patients (62%) were assessed at transplant as having chemosensitive disease, twenty-four patients (31%) were transplanted in the phase of chemoresistant disease (in 6, disease state at transplant was not known). Forty-eight (62%) patients were transplanted from an HLA identical sibling, 17 (22%) from a matched unrelated donor and 13 (17%) were transplanted from an unrelated donor with 1-2 allelic mismatches. The source of haematopoietic cells was bone marrow (BM) in 10 cases and peripheral blood progenitor cells (PBPC) in 68 cases. (Table 1)

Conditioning regimens. The following two tables list all the types of conditioning regimens used. Myeloablative and

Table 1. Patient characteristics

Pacient characteristics	N (%)
Total number of patients	78
Male	49 (63%)
female	29 (37%)
Histological diagnosis	
PTL*	8 (10%)
Hodgkin's lymphoma	18 (23%)
FL¶	17 (22%)
MCL‡	9 (12%)
DLBCL ∫	16 (20%)
Others	10 (13%)
Previous ASCT#	41 (53%)
Disease status at transplant	
chemosensitive	48 (62%)
chemoresistant	24 (31%)
NA	6 (7%)
Donor	
HLA matched related	48 (62%)
HLA matched unrelated (10/10)	17 (22%)
HLA 1-2 allelic – mismatched (9-8/10)	13 (17%)
PBPC/BM @	68 (87%)/10 (13%)

* PTL = peripheral T-cell lymphoma,. ¶ FL = follicular lymphoma, ‡ MCL = mantle-cell lymphoma , ∫ DLBCL = diffuse large B-cell lymphoma, # ASCT = autologous stem cell transplant, @ PBPC= peripheral blood progenitor cells , BM= bone marrow

Table 2. Preparative regimen- myeloablative

Regimen	n
busulphan + cyclophosphamide_(+/- ATG) *	14
cyclophosphamide + TBI¶ (+/- ATG)	2
cyclophosphamide + etoposide + TBI (+/-ATG)	1
fludarabine + busulphan (+/- ATG)	1

* ATG (Fresenius) = antithymocytary globuline, ¶ TBI = total body iradiation

Table 3. Preparative regimen – reduced – intensity

Regimen	n
fludarabine + busulphan 8mg/kg + ATG	18
fludarabine + melphalan (+/- ATG)	10
fludarabine + TBI 2Gy (+/- ATG)	3
fludarabine + cyclophosphamide (+/- ATG)	21
cyclophosphamide /ATG	2
BEAM* (+/- ATG)	2
idarubicine + fludarabine + busulfan (+/- ATG)	2
fludarabine + cisplatina + AraC¶ (+/- ATG)	2

* BEAM = BCNU, ethoposide, cytosin arabinoside, melphalan,
¶ AraC = cytosin arabinoside,

reduced intensity regimens are listed separately. Total body irradiation (TBI) was used in only nine patients (12%). Depending on the type of donor, in vivo T-cell depletion involved either rabbit anti-thymocyte globulin (ATG Fresenius), and the anti-CD 52 monoclonal antibody (Campath) was used in only 1 case.

The available data regarding immunosuppression for GVHD prevention could not be analysed. (Table 2 and 3)

Engraftment and peri-transplant toxicity. Engraftment occurred in 70 (90%) patients. One patient died early after transplantation and engraftment was not evaluable. In five patients transplanted using RIC, the absolute neutrophil count (ANC) never fell below 0.5 (x10.9/l). Two patients died of TRM without signs of engraftment. The median time to engraftment in evaluable patients was 16 days (7-31). Patients transplanted using PBPC had significantly faster engraftment in ANC than patients transplanted using BM (median 15 (7-24) days vs. 21 (15-31), p= 0.0001). We also noted only a trend towards better overall survival for PBPC (OS at 3 years 47% vs. 22%, p=0.06) and a trend towards lower incidence of cGVHD for BM (p=0.069). Neither the incidence of aGVHD or TRM differed significantly between the two groups. (Table 4)

A total of 26 patients died in relation to transplantation; twenty patients before day + 100 and 6 patients later, up to one year after transplant. Peri-transplant mortality up to day 100 was thus 26%, by 1 year 33%, and by 3 years 33% for the whole group, respectively 22%, 30% and 30% for the group transplanted with RIC and 39%, 44% and 44% in for the group transplanted myeloablatively. We evaluated a total of seven clinical variables from the aspect of TRM incidence (Table 5). Univariate analysis showed a significant difference only in the higher incidence of TRM in the group of chemoresistant patients (p=0.019).

GVHD. The incidence and severity of GVHD was relatively low, probably due to in vivo T-cell depletion using ATG in a majority of patients [for details, see lit. 13, 14, 15 when using regimens with Campath]. Acute GVHD developed in 26 (33%) patients, grade I-II in 17 cases, and grade III-IV in 9 cases. Forty-seven patients did not develop GVHD (data are missing in 5 cases). As to chronic GVHD, 53 patients were assessable, and chronic GVHD developed in 19 (36%) patients; of which 14 had a limited form, 3 an extensive form (in 2 patients we were unable to determine the extent from the data provided).

Donor lymphocyte infusion (DLI). Donor lymphocytes were administered following discontinuation of immunosuppression and in the absence of GVHD for reasons of disease relapse or progression in five patients (3xMCL, 2xHodgkin´s lymphoma). In four cases, lymphocytes from a matched sibling were used (1 patient developed grade II aGVHD but nonetheless died of relapse later on, 1 patient developed limited cGVHD and remains alive, another two patients are alive without signs of GVHD). In one patient, DLI from a matched unrelated donor were used and grade III aGVHD developed. This patient died of resistant relapse.

Survival results. At the last follow-up, 41 patients (53%) had died. Thirty-seven (47%) patients were alive, of which 33 (89%) were in complete remission, and the disease status was not known in 4. Of the 24 patients with chemoresistant disease at the time of transplant, 17 (71%) died (13 from TRM, 4 from relapse), 7 (29%) were alive, 5 in complete remission and disease status was not known in 2. Of the 48 patients with chemosensitive disease before transplant, 20

Table 4. Results comparison by graft type (PBPC vs BM)

	PBPC	BM	P
Engraftment ANC* (median)	15 (7-24) days	21 (15-31) days	**0,0001**
TRM	22/68	4/10	0,72
acute GVHD	22/66 (evaluable)	2/7 (evaluable)	0,7
chronic GVHD	19/47 (evaluable)	0/6 (evaluable)	0,069
OS at 3 years	47%	22%	0,06

ANC=absolute neutrophile count (x10.9/l), TRM= transplant-related mortality, GVHD = graft versus host disease,
OS = overall survival

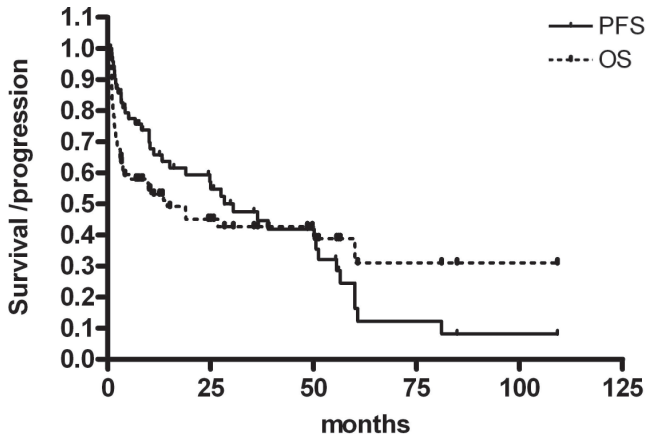

Figure 1. Probability of overall survival and progression-free survival

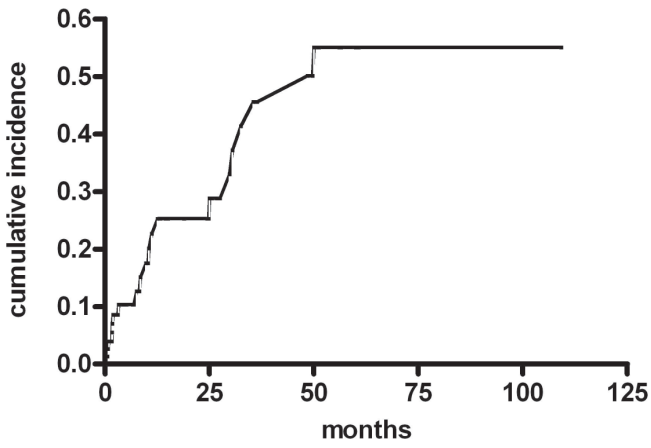

Figure 2. Relapse incidence

(42%) died (12 from TRM, 8 from relapse), 28 (58%) were alive, 26 (93%) in complete remission, and disease status was not known in 2. Six patients were not assessable from the aspect of chemo-sensitivity (4 died, 2 are alive in CR) (Table 6)

Relapse and progression. Relapse or progression following transplant occurred in a total of 20 (26%) patients: 6xDLCL, 2xHL, 7xFL, 2xPTL, 3x others. The cumulative incidence of relapse at 3 years for the whole group was 45%. (Fig. 2)

Comparison of results according to the conditioning regimen used. We analysed a total of 7 clinical variables on univariate analysis relating to both types of conditioning regimens used – myeloablative versus reduced intensity (Table 7). Significant differences between both types of regimens were found only related to age, whereby the median age of patients transplanted using RIC was 47 versus 40 in the group of patients transplanted myeloablatively (p=0.016).

OS and PFS. At the last follow-up, 37 (47%) patients were alive, median follow-up of 26 months (3-109). The 3-year OS was 44%, PFS 42% (Fig. 1). The 3-year OS for the individual histological subtypes was; 65 % for HL, 23% for DLBCL, 53% for FL, 32% for MCL, and 88% for PTL.

In relation to overall survival (OS), we evaluated 8 clinical factors (Table 8). On univariate analysis, survival of patients with PTL was significantly better than that of patients with DLBCL (p=0.01). Similarly, survival of patients with PTL was better compared to that of all the other histological variants (p=0.01) (Fig. 3). Both univariate and multivariate analysis then showed that another significantly better prognostic factor for overall survival was the disease status before transplant (3-years OS for chemo-sensitive disease is 56% vs.

Table 5. Univariate analysis of transplant-related mortality (TRM)

Factor	TRM/ overall number	(p)
Diagnosis		0,77
Hodgkin´s lymphoma	4/18	
Non-Hodgkin´s lymphoma	22/60	
Donor		1,0
matched related	16/48	
unrelated	10/30	
Disease status at SCT		0,019
chemosensitive	12/48	
chemoresistant	13/24	
untested	6	
Previous ASCT		1,0
yes	14/41	
no	12/37	
Acute GVHD		0,79
yes	8/26	
no	17/47	
NA	5	
Chronic GVHD		0,45
yes	4/19	
no	4/34	
not evaluable	25	
Conditioning		0,26
myeloablative	8/18	
reduced- intensity	18/60	

SCT= stem cell transplant, ASCT = autologous stem cell transplant, GVHD = graft versus host disease, NA (not aplicable)

Table 6. Response to treatment and follow-up (FU)

Disease status at SCT	n	Disease status at last FU/ alive	Death / cause
chemosensitive	48	28 (26 x CR, 2x NA)	20 (12x TRM, 8x relapse)
chemoresistant	24	7 (5 x CR, 2x NA)	17 (13x TRM, 4x relapse)
not known	6	2 x CR	4

SCT= stem cell transplant, TRM= transplant-related mortality, CR= complete remission

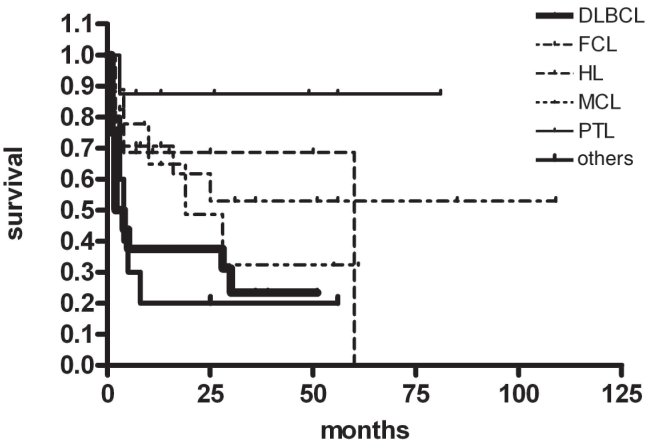

Figure 3. Survival by histological type

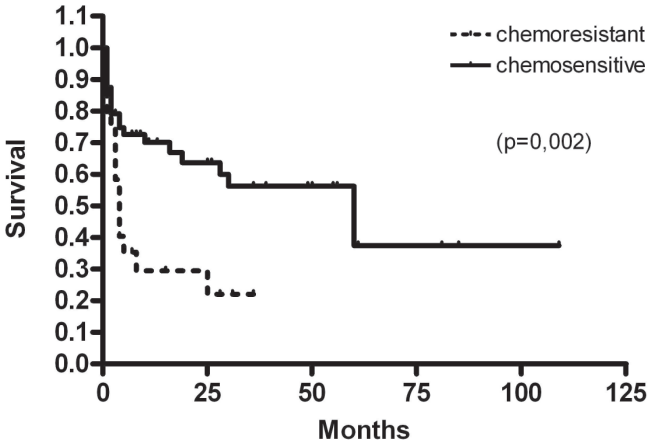

Figure 4. Survival by chemosensitivity

22% for chemo-resistant disease, p=0.002). (Fig. 4). No correlation between overall survival and any form of GVHD was observed. Similarly, we did not observe any significant difference when comparing the type of conditioning regimen used (OS at 3 years for MC 54% vs. 42% for RIC, p=0.9). The median age in the group transplanted with RIC was significantly higher, though, than in the group transplanted myeloablatively. No statistically significant difference was observed either according to the type of donor (OS at 3 years for IS vs. UD; 46% vs. 48%, in a group of comparable age). Also in our group, we did not observe worse survival in patients with a history of previous ASCT (OS at 3 years 35% following ASCT vs. 52% without ASCT, p= 0.14, again no significant difference between the age in both groups)

Discussion

The analysis presented here describes the results of allogeneic transplantation in patients with malignant lymphoma in the Czech Republic, focusing on the results of overall survival and attempting to identify prognostic factors for survival, relapse, peri-transplant mortality, as well as comparing the results of transplants following myeloablative vs. RIC conditioning.

Our analysis shows that in a significant proportion of patients, long-term disease control may be achieved (OS resp. PFS at 3 years 44% resp. 42%). Nonetheless, peri-transplant mortality remains relatively high (for the whole group 33% at 3 years, 30% for RIC and 44% for MC resp.)

We found a significant difference in survival between the individual histological subtypes only in the case of DLBCL vs. PTL (22% vs. 88%, p=0.01) and PTL versus all other subtypes. In view of the small number of patients (the PTL group included only 8 patients, 7 of whom were chemo-sensitive prior to SCT), these results probably cannot be interpreted reliably. Certain data in literature [16] points to a possible greater GVL effect in T-lymphomas, but this involved a selected group of patients.

TRM in patients with lymphoma transplanted myeloablatively corresponds to data in literature – both registry data [17, 10], as well as certain better defined groups [18]. This shows that a large proportion of patients die of complications associated with the transplant. Nonetheless, most of the patients who survive remain in complete remission on long-term follow-up. From the aspect of reduced intensity conditioning regimens, the incidence of TRM in our group is relatively high, nonetheless, it is still comparable with registry data [e.g. the largest EBMT analysis thus far, 19]. The problem faced when interpreting such results is the great heterogeneity of these groups in relation to the various histological subtypes, the various degree of prior treatment, and last but not least, various disease

Table 7. Univariate analysis by conditioning type

	RIC	Myeloablative	P
Age (median)	47 (21-63)	40 (19-64)	**0,016**
TRM	18/60	8/18	0,26
Previous ASCT	35/60	6/18	0,1
Chemosensitivity	36/55 (evaluable)	12/17 (evaluable)	0,77
Acute GVHD	18/60	8/18	0,26
Chronic GVHD	15/39 (evaluable)	4/11 (evaluable)	1,0
Numer of relapses	14/60	6/18	0,53

ASCT = autologous stem cell transplant, GVHD = graft versus host disease

status at transplant as well as the various conditioning regimens and variously intensive immunosuppression used. A number of recent studies refer about more encouraging results in better defined groups [MCL – 20, 21, LGL – 13, 22, Hodgkin – 23, 24], where it has been possible to reduce in a number of groups TRM in RIC below 10%.

In concurrence with published work, in our analysis the results of transplants from related and unrelated donors are comparable [1, 25].

The results of myeloablative allogeneic transplants in patients with prior failure of autologous transplantation are generally poor. A TRM of up to 80% [26] is cited in literature. It appears, though, that in patients transplanted using RIC, prior ASCT need not represent a significantly higher risk [20]. In our group, survival and TRM did not differ significantly between both types of transplant following ASCT.

In our group, we also compared the results of transplants conducted using peripheral blood cells (PBPC) collected following mobilisation with G-CSF (granulocyte colony stimulating factor) with those using bone marrow (BM) stem cells. PBPC usually contain more CD 34+ cells and thus enable faster engraftment than bone marrow. On the other hand, there are works that refer about the higher risk of chronic GVHD as a consequence of the approx. 10 times higher T-lymphocyte counts in the PBPC grafts [36, 37, 38]. The results of our analysis confirmed more rapid engraftment with PBPC, but we only noted a trend towards better OS for PBPC and a trend towards lower cGVHD incidence for BM.

One of the main potential advantages of allogeneic transplantation is the presumed so-called GVL effect. An extensive analysis of data from the IBMTR and EBMT [27] was published in 2003. This compared the results of allogeneic, syngennic and autologous transplantation in Non-Hodgkin lymphomas and did not show any GVL effect. There was no difference in the risk of relapse between allo and syngennic SCT. Moreover, the risk of relapse did not correlate either with acute GVHD, chronic GVHD or T-cell depletion. According to other sources, the effect of DLI was also not proven in aggressive NHL [28, 29]. Nonetheless, there exist works that support the response to DLI in other histological types, e.g. follicular lymphoma [30, 13, 31] or Hodgkin's lymphoma [32]. In our group, DLI were used five times, but we did not observe clear correlation with a GVL effect. Similarly, we did not observe a significant difference in OS or PFS between the sub-groups with aGVHD or cGVHD, compared to patients with no signs of graft-versus-host disease.

As expected and supported by many works [33, 34, 20], disease chemosensitivity at the time of allo-SCT was a significantly favourable factor for overall survival and relapse rate. Patients who responded to chemotherapy prior to allo-SCT had a significantly superior OS (56% vs. 22% at 3 years, p=0.002), and PFS (52% vs. 23%, p= 0,008).

On multivariate analysis, chemosensitive disease and female sex appeared to be a significantly favourable factor.

Table 8. Univariate and multivariate analysis of overall survival (OS)

Factor	Number	Univariate analysis 3-years OS (CI 5-95%) (p)	Multivariate analysis (p)
Age at SCT		ns	ns
less than 50 years	53		
more than 50 years	25	52% 35%	
Diagnosis			ns
PTL	8	88% 0,01	
DLCL	16	23% ns	
FL	17	53% ns	
HL	18	65% ns	
MCL	9	32% ns	
Others	10	20% ns	
Donor		ns	ns
matched related	48	46%	
unrelated	30	48%	
Disease status at SCT		0,002	0,015
chemosensitive	48	56%	
chemoresistant	24	22%	
untested	6		
Previous ASCT		ns	
yes	41	35%	
no	37	52%	-
Acute GVHD		ns	-
yes	47	50%	
no	26	40%	
NA	5		
Chronic GVHD		ns	ns
yes	19	64%	
no	34	39%	
not evaluable	25		
Conditioning		ns	ns
myeloablative	18	54%	
reduced intensity	60	42%	
Sex		ns	0,026
female	29	53%	
male	49	40%	

SCT= stem cell transplant, ASCT = autologous stem cell transplant, GVHD = graft versus host disease, PTL = peripheral T-cell lymphoma, FL = follicular lymphoma, MCL=mantle-cell lymphoma, DLBCL = diffuse large B cell lymphoma

In conclusion, it may be said that, based on our data, allogeneic transplantation may lead to long-term disease control in around 40% of patients with relapsing lymphoma. Peri-transplant mortality in an un-selected population remains relatively high, 30-40%, according to the conditioning regimen used. The only remaining problem are patients with chemoresistant disease in whom, probably, allogeneic transplantations is only of limited significance. Our analysis did not show any correlation between the incidence of GVHD and a lower incidence of relapse that would support the importance of a GVL effect. Our group is too heterogeneous and the number of patients in the individual sub-groups is too small to enable a more detailed analysis of the results of this method in individual histological subtypes of malignant lymphomas and of the advantages and disadvantages of various conditioning regimens.

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