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Allogeneic or autologous stem cell transplantation (SCT) for relapsed and refractory Hodgkin's disease and non-Hodgkin's lymphoma: a single-centre experience

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Abstract: *Purpose of the study:* The aim of the study was to evaluate which patient might benefit most from allogeneic stem cell transplantation (SCT) in the treatment of relapsed and/or refractory lymphoma. *Patients and methods:* Thirty-eight consecutive lymphoma patients receiving either autologous ($n=24$) or allogeneic ($n=14$) stem cell grafts at our institution from 1986 to 1998 were retrospectively analysed regarding overall survival (OS), disease-free survival (DFS), transplant-related mortality (TRM), and relapse incidence (RI). Uni- and multivariate analyses were performed to identify patient characteristics predictive for outcome after SCT. *Results:* The probabilities of OS, DFS, TRM, and relapse were 57%, 51%, 29%, and 30% following autologous and 43%, 43%, 29%, and 38% following allogeneic SCT. Disease status (sensitive versus refractory) and the time interval between diagnosis and SCT were the most powerful predictive parameters for OS and TRM, whereas elevated serum LDH levels were signifcant in determining relapse. *Conclusions:* In patients with elevated serum LDH levels and bone marrow involvement at the time of transplantation allogeneic was superior to autologous SCT and resulted in better outcome due to a lower relapse incidence strongly suggesting the existence of a graft-versus-lymphoma effect.

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Key words: stem cell transplantation (SCT); graft-versus-lymphoma (GVL) effect; Hodgkin's disease (HD); non-Hodgkin's lymphoma (NHL)

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High-dose chemo/radiotherapy with autologous stem cell rescue offers a reliable chance of long-term disease-free survival for patients with relapsing or refractory Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL) who otherwise have a poor prognosis (1–4). During the past decade several studies have demonstrated the relative effectiveness of this approach and its advantages over conventional-dose salvage regimens in selected patients (5–9). In contrast, allogeneic SCT is used only sporadically because of its higher TRM and the risk of developing acute and/or chronic graft-versus-host disease (GVHD) (10–17). Potential graft-versus-lymphoma (GVL) effects associated with allogeneic SCT are supposed in some series but warrant confirmation by prospective, randomized trials (18–21). To define better the role of allogeneic SCT in the management of poor-risk lymphoma we here report on our experience obtained in 38 consecutive patients transplanted at our institution from 1986 to 1998.

Patients and methods

Patients

Between 1986 and 1998, 38 patients (HD, $n=14$; NHL, $n=24$) received either autologous ($n=24$) or

allogeneic, HLA-identical ($n=14$) stem cell grafts. Preference was generally given to an allograft when patients were candidates for both types of graft. All patients were classified as having poor prognosis defined as either primary refractory or achieving only partial recovery (PR) after initial standard treatment, or as disease relapsing within one year from diagnosis after achieving complete remission (CR) following initial chemotherapy, or as patients with second or subsequent relapse. Patients with NHL were classified according to the updated Kiel classification and patients with HD according to the Rye classification (22, 23). Patient characteristics are detailed in Tables 1 and 2.

Preparative regimens and stem cell infusion

For patients with previous dose-limiting radiation therapy the standard preparative regimen was high-dose cyclophosphamide, carmustine, and etoposide (CBV, consisting of 100 mg/kg CY, 15 mg/kg BCNU, and 60 mg/kg etoposide) followed by either autologous ($n=15$) or allogeneic ($n=2$) SC infusion (24). Patients without prior dose-limiting radiotherapy received a combination of high-dose CY (100 mg/kg), etoposide (60 mg/kg), and fractionated TBI (fTBI, 12 Gy, given in six fractions over three consecutive days) followed by either allogeneic ($n=6$) or autologous ($n=9$) SCT. Standard high-dose CY(120 mg/kg) plus fTBI (12 Gy) was given prior to five allogeneic and one autologous SCT. One patient received a combination of BU (8 mg/kg), CY (100 mg/kg), and single-dose TBI (10 Gy) followed by allogeneic stem cell infusion.

Allografted patients received a median of 3.41 (range 2.1–6.2) $\times 10^8$/kg BM nucleated cells from their HLA-identical sibling donors and autografted patients were reinfused with a median of 0.37 (range 0.19–0.47) $\times 10^8$/kg BM plus a median of 2.52 (range 0.18–4.34) $\times 10^8$/kg PBMC obtained by means of steady-state leukapheresis ($n=9$). Since 1995 patients undergoing autologous SCT were reinfused with either $\geqslant 4.0 \times 10^8$/kg unmodified PBMC or $\geqslant 2.0 \times 10^6$/kg immunoselected (Cell-Pro) CD34+ hematopoietic stem cells mobilised with either high-dose CY (4–7 g/m^2, $n=12$) or DHAP ($n=3$) plus G-CSF according to recently published standard procedures (25).

Relapse prophylaxis

Patients with radiological (CT scan) evidence of localised disease at the time of SCT underwent involved-field irradiation (20–30 Gy) starting as soon as possible within the first three months after hematopoietic regeneration.

Supportive care including graft-versus-host disease prophylaxis

Patients receiving autologous SCT were treated under strict reverse isolation without laminar airflow. Patients receiving allografts were nursed in

Table 1. Patient characteristics I

	Allogeneic SCT ($n=14$)	Autologous SCT ($n=24$)
Median age (yr, range)	35 (16–48)	41 (16–55)
Female:male ratio	6:8	7:17
Primary diagnosis		
Hodgkin's disease	5 (36%)	9 (37%)
Non-Hodgkin's lymphoma	9 (64%)	15 (63%)
Low-grade	2 (22%)	8 (53%)
High-grade	7 (78%)	7 (47%)
Median time from diagnosis to SCT (months, range)	17 (3–62)	26 (6–117)
Disease status at SCT		
Sensitive	6 (43%)	15 (62%)
Refractory/progressive	8 (57%)	9 (38%)
Number previous lines of treatment		
1–2	8 (57%)	9 (38%)
$\geqslant 3$	6 (43%)	15 (62%)
Time from diagnosis to SCT		
$\leqslant 3$ yr	11 (79%)	15 (62%)
>3 yr	3 (21%)	9 (38%)
Serum LDH levels at SCT		
$\leqslant 240$ IU/L	11 (79%)	19 (79%)
>240 IU/L	3 (21%)	5 (21%)
Bone marrow involvement at SCT		
No	10 (71%)	17 (71%)
Yes	4 (29%)	7 (29%)
Age at SCT		
$\leqslant 40$ yr	11 (79%)	11 (46%)
>40 yr	3 (21%)	13 (54%)

Table 2. Patient characteristics II

	Allogeneic SCT ($n=14$)	Autologous SCT ($n=24$)
Median observation time following SCT (months, range)	18 (0–132)	25 (0–154)
Median follow-up for patients alive (months, range)	106 (39–132)	45 (11–154)
Conditioning regimen		
CBV	2	15
CY/fTBI	5	1
BUCY/TBI	1	0
CY/VP-16/fTBI	6	8
TBI-containing	12 (86%)	9 (38%)
G-CSF after Tx	3 (21%)	22 (92%)
Median days until leukocytes >1.0 G/L (range)	16 (12–29)	15 (9–37)
GVHD prophylaxis		
CsA	11	–
CsA/MTX	3	–

laminar airflow rooms from the beginning of the conditioning regimen until hematopoietic regeneration. No prophylactic systemic antibiotics were administered. All patients underwent a non-absorbable oral gut decontamination with vancomycin, gentamycin, and nystatin. *Pneumocystis carinii* prophylaxis was performed with trimethoprim-sulfamethoxazole given in a 10-d course before transplantation and after the take. Cytomegalovirus (CMV) pneumonia prophylaxis consisted of infusions of CMV hyperimmunoglobulin (Cytotect, Cutter, 1 ml/kg) every other week until day $+100$. Irradiated (25 Gy), leukocyte-depleted and CMV-negative red cells and platelet transfusions from single donors were administered when hemoglobin levels were 7.0 g/dL or less and platelets were 20 G/L or less. To accelerate hematopoietic regeneration G-CSF (5 μg/kg/d) was given to 3/14 (21%) allografted and to 22/24 (92%) autografted patients starting on the day after SC infusion.

GVHD prophylaxis consisted of cyclosporine A (CsA) alone ($n=11$) or in combination with short-course methotrexate (MTX) according to the Seattle protocol ($n=3$). Grading and treatment of acute and chronic GVHD was performed according to the standard Seattle criteria and protocols.

Statistics

Survival analyses were performed according to the method of Kaplan and Meier (26). Overall survival (OS) was calculated from the date of SCT to the date of death from any cause or day of last follow-up. Disease/progression free survival (DFS) was calculated from the date of SCT to the date of documented disease relapse/progression. Transplant-related mortality was defined as the probability of death without relapse or disease progression. For two patients receiving a second graft (one autologous and one allogeneic) because of disease progression/relapse after autologous SCT the unit studied was the patient and the censored data correspond to the date of the last contact for each patient according to the recently published European Group for Blood and Marrow Transplantation (EBMT) statistical guidelines (27).

Univariate analysis of the following parameters was performed using the log-rank test and SPSS software to identify patient characteristics predictive for outcome after SCT: diagnosis (HD vs. NHL), stem cell source (allogeneic vs. autologous), disease status at the time of SCT (SD vs. RD/PD), conditioning regimen (TBI-containing vs. chemotherapy alone), number of previous lines of treatement (1–2 vs. $\geqslant 3$), BM involvement at the time of SCT (yes vs. no), and serum LDH levels at the time of SCT ($\leqslant 240$ IU/L vs. >240 IU/L). For the variable "age" the median age (40 yr) of the whole study population was chosen as cut-off. For the variable "time interval between diagnosis and SCT" an interval of 3 yr was chosen because the greatest difference in overall survival was observed between patients receiving a transplant within or beyond this time frame.

Multivariate analysis was performed using Cox's proportional hazards model. The factors examined were the same as those included in the univariate analysis.

Results

Hematological engraftment, overall survival (OS), and disease-free survival (DFS)

All but four patients dying too early because of regimen-related toxicity and/or infection engrafted (defined as the first day with a persistent leukocyte count >1.0 G/L) after a median of 16 d (range 12–29) following allogeneic and a median of 15 d (range 9–37) following autologous SCT.

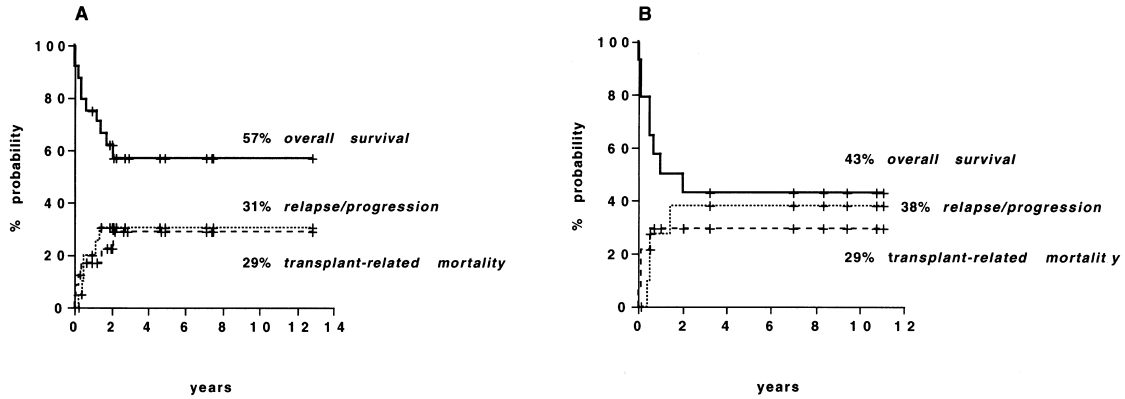

Fig. 1. Probabilities of overall survival (OS), relapse/progression and transplant-related mortality following autologous (A) or allogeneic (B) stem cell transplantation for poor-risk lymphoma.

The probability of OS $\pm$95% confidence interval (CI) for all patients was 51 $\pm$ 8% with an actuarial survival at 3 yr of 57 $\pm$ 11% vs. 43 $\pm$ 13% following autologous vs. allogeneic SCT (Fig. 1) and a disease/progression-free survival of 51 $\pm$ 10% vs. 43 $\pm$ 13%.

The most powerful predictive parameters for survival following SCT were disease status and time interval from diagnosis to SCT ($p \leqslant 0.05$, log-rank test, Fig. 2 and Table 3). Younger age, non-TBI-containing conditioning, normal serum LDH levels, and absence of bone marrow involvement were also associated with improved survival but did not reach statistical significance (Table 3).

Allogeneic SCT was superior to autologous SCT only in patients with elevated serum LDH levels $>$240 IU/L (overall survival 33 $\pm$ 27% vs. 20 $\pm$ 18%, difference not significant) and BM involvement at the time of SCT (overall survival 75 $\pm$ 22% vs. 0%, $p = 0.091$) mainly due to a lower RI.

For HD patients, OS following allogeneic vs. autologous SCT was 40 $\pm$ 22% vs. 67 $\pm$ 15%. For patients with NHL, survival following allogeneic and autologous SCT was 44 $\pm$ 17% and 47 $\pm$ 15%, respectively. Overall survival following autologous SCT was 42 $\pm$ 21% for patients with low-grade lymphoma vs. 57 $\pm$ 16% for high-grade lymphoma.

Survival for patients with sensitive disease receiving allografts and autografts was 67 $\pm$ 21% and 78 $\pm$ 18%, respectively, whereas survival in patients with refractory disease was only 25 $\pm$ 13% following allo- and 22 $\pm$ 12% following autotransplantation (differences not significant). Also for all other variables listed in Table 3 survival was not different between auto- and allotransplantation.

Relapse incidence (RI) and graft-versus-host disease (GVHD)

The probability of relapse/progression ($\pm$95% CI) at 3 yr for the entire study cohort was 34 $\pm$ 9%, with a RI of 38 $\pm$ 15% vs. 31 $\pm$ 11% following allogeneic vs. autologous SCT (Fig. 1).

The only factor significantly determining RI was serum LDH level with a significantly higher RI in patients with elevated serum LDH levels (71 $\pm$ 23% vs. 25 $\pm$ 9%, $p = 0.048$, Table 3). Also patients with refractory disease had a higher RI (51 $\pm$ 17% vs. 25 $\pm$ 10%), but this did not reach statistical significance (Fig. 2, Table 3).

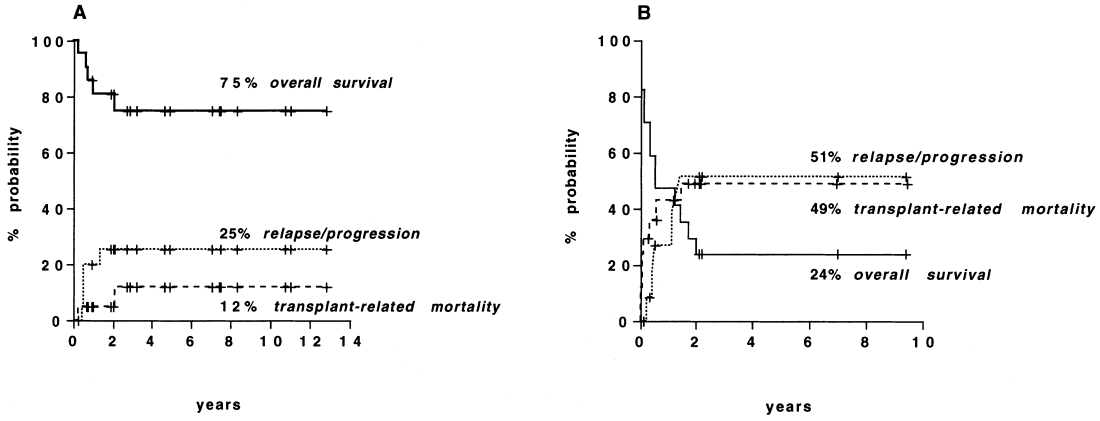

Fig. 2. Probabilities of overall survival (OS), relapse/progression and transplant-related mortality following stem cell transplantation for poor-risk lymphoma with sensitive (A) or refractory/progressive disease (B).

Table 3. Uni-(log-rank test) and multivariate (Cox model) analysis of prognostic variables for overall survival, relapse incidence, and transplant-related mortality following SCT for poor-risk lymphoma ($n=38$)

		Overall survival (OS)				Relapse incidence (RI)				Transplant-related mortality (TRM)			
Prognostic variables	Patients at risk	(% ± SD)	Log-rank	Cox model	Odd's ratio	(% ± SD)	Log-rank	Cox model	Odd's ratio	(% ± SD)	Log-rank	Cox model	Odd's ratio
Type of SCT													
Autologous	24	56 ± 11				31 ± 11				29 ± 11			
Allogeneic	14	43 ± 13	0.42	0.4814	1.70	38 ± 15	0.7652	0.7392	1.40	29 ± 12	0.8138	0.1882	4.70
Age at SCT													
⩽40 yr	22	59 ± 10				34 ± 11				23 ± 9			
>40 yr	16	36 ± 14	0.361	0.8742	0.90	34 ± 14	0.8779	0.9848	1.00	44 ± 18	0.5154	0.6121	0.70
Diagnosis													
Hodgkin's disease	14	57 ± 13				39 ± 15				29 ± 12			
Non-Hodgkin's lymphoma	24	48 ± 11	0.6499	0.6351	1.40	31 ± 10	0.7989	0.7858	1.30	30 ± 11	0.8649	0.2611	0.20
Conditioning													
Chemotherapy	17	64 ± 11				29 ± 12				18 ± 9			
TBI-containing	21	42 ± 11	0.2439	0.4392	1.60	38 ± 12	0.639	0.9757	1.00	37 ± 12	0.3191	0.3043	2.60
Disease status at SCT													
Sensitive	21	75 ± 10				25 ± 10				12 ± 8			
Refractory/progressive	17	24 ± 10	**0.0003**	**0.0099**	**7.80**	51 ± 17	0.189	0.4205	2.30	49 ± 12	**0.0033**	**0.034**	**19.00**
Previous lines of treatment													
1–2	17	50 ± 13				33 ± 12				30 ± 14			
⩾3	21	51 ± 11	0.8839	0.424	0.50	34 ± 13	0.8014	0.738	0.70	29 ± 10	0.687	0.08	0.10
Time from diagnosis to SCT													
⩽3 yr	26	60 ± 10				30 ± 9				19 ± 8			
>3 yr	12	33 ± 14	**0.0438**	**0.0724**	**3.90**	49 ± 20	0.8014	0.925	1.10	50 ± 14	**0.013**	**0.016**	**34.80**
Serum LDH levels at SCT													
⩽240 IU/L	30	58 ± 10				25 ± 9				26 ± 9			
>240 IU/L	8	25 ± 15	0.0714	0.8949	0.90	71 ± 23	**0.048**	**0.1896**	**3.60**	43 ± 19	0.456	0.3029	0.50
BM involvement at SCT													
No	27	59 ± 10				36 ± 10				19 ± 8			
Yes	11	34 ± 15	0.2108	0.6096	0.70	27 ± 17	0.5689	0.1923	0.20	52 ± 18	0.0966	0.4976	2.60

There was a trend for a lower RI following allotransplantation in patients with elevated serum LDH levels (33 ± 15% vs. 73 ± 22% for autologous transplantation, difference not significant) and in patients with BM involvement (0% vs. 47 ± 15% for autologous transplantation, difference not significant). We also observed a trend for a lower RI in HD patients following allotransplantation (33 ± 27% vs. 43 ± 19% following autologous SCT), whereas for NHL patients the incidence of relapse following allogeneic SCT was even higher than following autologous SCT (43 ± 19% vs. 24 ± 12%), but there were more high-grade lymphomas in the allogroup (78% vs. 47%). For none of the variables listed in Table 3 was relapse incidence significantly different between allo- and autotransplantation.

Acute GVHD (aGVHD) grades I–II developed in 7/14 allografted patients after a median of 22 (1–27) d. None of the patients developed aGVHD grades III–IV or died due to GVHD, and only one patient had laboratory signs of limited chronic GVHD of the liver requiring prolonged administration of CsA. Interestingly, 4/7 allografted patients without aGVHD died of relapse/progression, whereas none of the allografted patients with evidence of aGVHD relapsed within the study period.

Transplant-related mortality (TRM) and causes of death

Eighteen patients died within the observation period. The causes of death in the allogroup were relapse/progression ($n=4$), viral interstitial pneumonitis ($n=3$), and septical multiorgan failure ($n=1$), whereas in the autogroup three patients died of relapse/progression, six patients due to infectious complications and one patient died of cardiac toxicity.

Sensitivity of disease and disease duration were the only variables associated with a significantly lower TRM following SCT (Table 3).

As shown in Fig. 1, TRM was similar following allogeneic and autologous SCT. There was a trend for a higher TRM in patients with HD receiving allografts (40 ± 22% vs. 22 ± 14% following autologous SCT, difference not significant).

For all other variables listed in Table 3 no significant differences in TRM between allogeneic and autologous SCT were observed.

Discussion

In accordance with other reports, sensitive disease was the most powerful predictive parameter for survival after SCT for poor-risk lymphoma (2–5,

14, 15, 21). Additionally, our data demonstrate that a shorter disease duration was associated with favourable outcome, indicating that high-dose chemotherapy with stem-cell support should be offered early to patients with relapsing and/or refractory lymphoma. As suspected, for both variables the better outcome resulted from a significantly lower transplant-related mortality not only following autologous but also allogeneic SCT.

To date there is no answer to the question of which lymphoma patient should receive and would benefit most from allogeneic SCT if both treatment modalities are available. Although there is some evidence supporting the concept of a graft-versus-lymphoma (GVL) effect at least in selected subgroups, so far no prospective study has proved any survival advantage of allogeneic over autologous SCT because of a higher procedure-related mortality (10, 18–21).

Although in our study differences between auto- and allotransplantation with regard to any of the variables tested by uni- and multivariate analysis were statistically not significant because of the small patient numbers in the individual subgroups, the improved survival due to a lower relapse incidence following allotransplants in patients with elevated serum LDH levels and bone marrow involvement at the time of SCT supports the hypothesis of a GVL effect. Whether such an effect also exists in Hodgkin's disease as supposed from the lower RI found in HD patients receiving allografts remains to be shown. Irrespectively, the fact that none of the allografted patients developing clinical GVHD relapsed compared with 4/7 patients without GVHD strongly argues in favour of the existence of either tumor-specific (tumor antigen-directed) or unspecific (minor antigen-directed) antitumor effects mediated by the graft. Interestingly, in contrast to other published series we did not find a higher treatment-related mortality following allografting with the exception of HD patients, but this difference did not reach statistical significance (18, 20, 21). Nonetheless, treatment-related mortality remains high and accounted for 50% of all deaths in the allogroup and for 70% of all deaths in the autogroup, and was definitively only acceptable in patients with sensitive disease. Whether graft manipulation by either T-cell depletion or $CD34^+$ selection with or without graded T-cell add-back can overcome these shortcomings at least in the allogeneic setting of SCT without any negative effect on relapse/progression or infectious complications remains to be seen (28).

Disease relapse/progression is the second major factor contributing to treatment failure following both types of SCT. All but one relapsing patient receiving a second autologous transplant died within weeks to months due to progressive disease, requiring alternative treatment strategies for those patients. Donor lymphocyte infusions (DLI) alone or in combination with chemotherapy might work after allogeneic SCT as shown by some recent reports but are far from being successful in all relapsing patients (29, 30). Recurrence after autologous SCT might be effectively salvaged by allogeneic or a second autologous SCT with acceptable toxicity, but long-term outcome remains poor (31, 32).

In conclusion, our results support the existence of a graft-versus-lymphoma effect and identify patients with elevated serum LDH levels and bone marrow involvement as those patients who might benefit most from allogeneic SCT when using standard procedures. The results, however, are preleminary and must be interpreted with caution due to the small patient number unless they have been confirmed by larger prospective, randomized studies. Recent advances especially the introduction of alternative, less toxic treatment modalities such as non-myeloablative conditioning will help to reduce toxicity and to clarify the mechanisms involved in graft-versus lymphoma effects and will inevitably increase the number of allogeneic transplants in the treatment of malignant lymphoma (33, 34).

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