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Autologous Transplant

Factors associated with survival in patients with progressive disease following autologous transplant for lymphoma

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Summary:

Our objectives were to assess survival and predictors for survival among lymphoma patients whose disease had progressed after autologous bone marrow (ABMT) or stem cell transplantation (ASCT). Patients transplanted at Hadassah University Hospital between October 1983 and February 1999 were included. We compared survival of patients with Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) after relapse or progression. Predictors for survival were assessed in a multivariate model. Of 88 transplanted patients with HD and 152 with NHL, relapse/progression occurred in 27 (31%) and 75 (49%), respectively. Median survival postrelapse was 25 months for HD and 7.5 months for NHL ($P = 0.12$). Seven relapsed patients with HD (26%) and 10 (13%) with NHL survived >4 years. In NHL, longer postrelapse survival was associated with indolent histologies ($P = 0.007$). On multivariate analysis, factors associated with survival included attainment of remission postrelapse (for both diseases), use of prophylactic immunotherapy (for HD), LDH level and time from transplant to relapse (for NHL). The short-term prognosis for patients with disease progression postautologous transplant may be somewhat better for HD compared to NHL. Long-term survival is poor in both diseases. However, the survival times in the current study are twice as long as those previously reported. Treatment regimens with the potential for achieving remission may have an impact on survival.

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Introduction

Despite successes with initial chemotherapy regimens, approximately two-thirds of lymphoma patients are eventual candidates for salvage therapy.[1] Some are treated with localized radiation or conventional chemotherapy regimens, but increasingly, eligible patients who relapse after primary treatment are referred for high-dose therapy options with stem cell rescue. These regimens have been shown to be superior to standard chemotherapy in terms of progression-free survival in Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) patients, especially those with chemotherapy-responsive relapse,[2–4] although their role in prolonging overall survival has recently been questioned.[5]

Unfortunately, despite great promise, high-dose therapies are not definitive. Relapse or disease progression within 5 years after autologous stem cell (ASCT) or bone marrow transplant (ABMT) occurs in 41%[3] of cases of HD and 54%[2] of NHL patients with chemosensitive relapses according to clinical trial data. Clinicians therefore encounter an increasing number of patients who have failed both frontline and high-dose salvage regimens, for whom no clear treatment guidelines exist.[6] Surprisingly, the literature is sparse on this subject and there have been few systematic studies devoted to this problem. Our clinical impression was that some patients, especially those with HD whose disease had progressed post-transplant, had a relatively prolonged clinical course, their disease often exhibiting indolent behavior, which would not have been predicted from their pretransplant course.

We reviewed the survival and prognostic characteristics of all patients who underwent autologous transplantation (stem cell or bone marrow) at Hadassah University Hospital in Jerusalem and whose disease had progressed following high-dose therapy. Our aims were to describe the clinical features of this patient population and compare the survival and prognostic factors in patients with HD *vs* those with NHL.

Patients and methods

All patients who underwent autologous peripheral blood stem cell or bone marrow transplant (hereafter ASCT) for HD and NHL between 1 October 1983 and 28 February

1999 were eligible for inclusion in the study. We examined medical charts, computerized hospital databases and contacted referring physicians to assess the patients' current status and verify whether relapse or disease progression had occurred. We accessed the Ministry of Interior Population Registry for information on vital status of the patients. Minimum follow-up post-transplant was 1 year. For details of treatment after relapse, we consulted medical charts, the computerized cytotoxic drug therapy database in our hospital and patients' treating physicians. All data extraction from charts was performed by one reviewer (CR).

Statistical analysis

All statistical analyses were performed using SPSS for Windows version 10 (SPSS, Chicago, IL).

Differences in proportions were assessed using the χ^2 test, and differences in means using the *t*-test. Kaplan–Meier survival curves were generated and compared using the log-rank test.[7] Prognostic factors for survival were assessed using a Cox proportional hazards model.[8] Factors found to be significantly associated with survival on univariate analysis were entered into a multivariate Cox model. The criterion for variable entry was $P<0.10$. Backwards selection was used to determine the final models. For all analyses a two-sided *P*-value of $\leqslant 0.05$ was considered statistically significant.

Results

During the study period, a total of 240 patients with lymphoma, 88 with HD and 152 with NHL underwent ASCT at our center. The source of stem cells was exclusively bone marrow until 1990. Between 1990 and 1995 there was increasing use of peripheral blood stem cells. Since 1995 GCSF-mobilized peripheral blood stem cells were used almost exclusively. Patient and transplant characteristics are shown in Table 1.

There was a male preponderance with HD. More patients with HD than with NHL were transplanted with active disease (39 *vs* 25%). The conditioning regimen varied during the study period, but in >90% of cases contained etoposide, cytosine arabinoside and melphalan. Overall 30-day post-transplant mortality was 5%. A total of 13 patients received post-transplant allogeneic cell-mediated and cytokine-activated immunotherapy.[9]

The relapse-free survival of both HD and NHL patients is shown in Figure 1. In all, 27 of the 88 HD patients (31%) relapsed or progressed post-transplant, while for NHL the proportion was 75 of the 152 (49%). Relapse-free survival was significantly better for HD compared to NHL ($P=0.004$). The occurrence of disease progression post-transplant was not associated with remission status at transplant in HD, whereas for patients with NHL, those who entered transplant in complete remission had a lower probability of relapse (hazard ratio (HR) 2.04, 95% confidence interval (CI): 1.19–3.52 for partial remission compared to complete remission and 3.13 (1.69–5.8) for active disease compared to complete remission). The

Table 1 Characteristics of 240 lymphoma patients undergoing ASCT 1983–1999

Variable	*Hodgkin's, N=88*	*Non-Hodgkin's, N=152*
Sex		
Male	64 (73%)	82 (54%)
Female	24 (27%)	70 (46%)
Diagnosis to transplant		
⩽12 months	9 (10%)	44 (29%)
13–24 months	29 (33%)	55 (36%)
25–60 months	31 (35%)	36 (24%)
>60 months	19 (22%)	16 (10%)[a]
Status at transplant		
CR	23 (26%)	56 (37%)
PR	31 (35%)	58 (38%)
Active disease	34 (39%)	38 (25%)
Prior chemotherapy regimens		
1	46 (52%)	73 (48%)
2	12 (14%)	28 (18%)
3+	30 (34%)	51 (34%)
Source of stem cells		
Bone marrow	64 (73%)	85 (56%)
Peripheral blood[b]	24 (27%)	67 (44%)
Conditioning regimen		
BECAM	12 (14%)	10 (6%)
BETCAM	20 (23%)	17 (11%)
TECAM[c]	53 (60%)	115 (76%)
OTHER	3 (3%)	10 (7%)
30-day post-transplant mortality	5 (6%)	7 (5%)

[a]One case unknown.
[b]Nearly all since 1995.
[c]Etoposide: 200 mg/m^2, days –6 to –3; thiotepa: 40 mg/m^2, days –5 to –2; cyclophosphamide: 60 mg/kg, day –3; ara-c: 200 mg/m^2, days –4 to –1; melphalan: 60 mg/m^2, days –2 and –1 (BETCAM includes addition of BCNU and BECAM includes BCNU but does not include thiotepa).

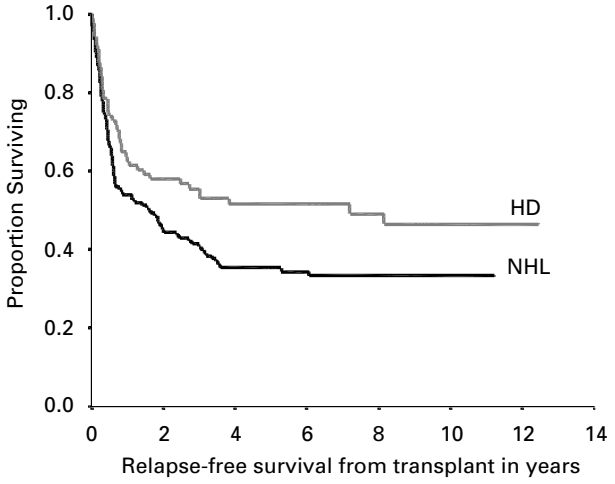

Figure 1 Relapse free survival for lymphoma patients who underwent autologous transplant 10/83–2/98. The upper curve (grey) represents HD, and the lower curve (black) represents NHL. The difference in survival functions was statistically significantly ($P=0.004$) by log-rank test.

Table 2 Characteristics of lymphoma patients whose disease relapsed or progressed following autologous transplant

Variable	*Hodgkin's (27 of 88 = 31%)*	*Non-Hodgkin's (75 of 152 = 49%)*	*P-value*
Status at transplant			
CR	6 (22%)	22 (29%)	0.39
PR	10 (37%)	33 (44%)	
Active disease	11 (41%)	20 (27%)	
Site of relapse			
Original site	11 (41%)	27 (36%)	0.75
New site	6 (22%)	14 (19%)	
Widespread	10 (37%)	34 (45%)	
Median survival post-transplant	Not reached (mean 8 years)	4.4 years (mean 6 years)	0.04
Median survival since relapse or progression	25 months	7.5 months	0.12
Received prophylactic post-transplant immunotherapy	11 (41%)	37 (49%)	0.44
Treatment postrelapse			
Chemotherapy	18 (67%)	51 (68%)	0.9
Radiotherapy	8 (30%)	20 (27%)	0.77
Immunotherapy	4 (15%)	21 (28%)	0.17
Second transplant	4 (15%)	5 (7%)	0.2
Currently alive	10 (37%)	20 (27%)	0.3

median time to relapse or progression for patients with HD was not reached (mean 8.27 years, 95% CI: 7–9.5 years), whereas for NHL it was 2.8 years (mean 5.3 years, 95% CI: 4.42–6.18 years). There was an inverse relation between time to relapse or progression and the aggressiveness of the histology for NHL patients (according to the International Working Formulation).[10] Median time to progression was 193 days for high-grade, 219 days for intermediate-grade and 314 days for low-grade lymphoma. Most relapses were either widespread or at the original site of disease (Table 2). In all, 48 relapsed patients received prophylactic post-transplant immunotherapy with alpha interferon, with or without interleukin 2.[11]

The main aim of the study was to examine survival in relapsed patients: The median survival from relapse or disease progression was 7.5 months for NHL and 25 months for HD (Figure 2). The difference between these survival curves was not statistically significant ($P = 0.12$) by the log-rank test. Median survival post-transplant was 4.2 years for relapsed patients with HD and 1.6 years for those with NHL. This is in contrast with a median survival of >11 years for nonrelapsed patients in both disease categories. For relapsed patients with NHL, histology was a strong predictor of survival (Figure 3). In those with high-grade histology, death occurred within a few months (median survival 4 months) *vs* several years for low-grade histologies (median survival not reached, $P = 0.007$).

Relapsed patients received a variety of treatments (see Table 2). A total of 17 (23%) patients with NHL and five (19%) with HD received supportive care only. The others received a variety of treatments including chemotherapy (multiple regimens), immunotherapy and radiation therapy. A surprisingly large proportion of patients attained a partial or complete remission with post-transplant salvage

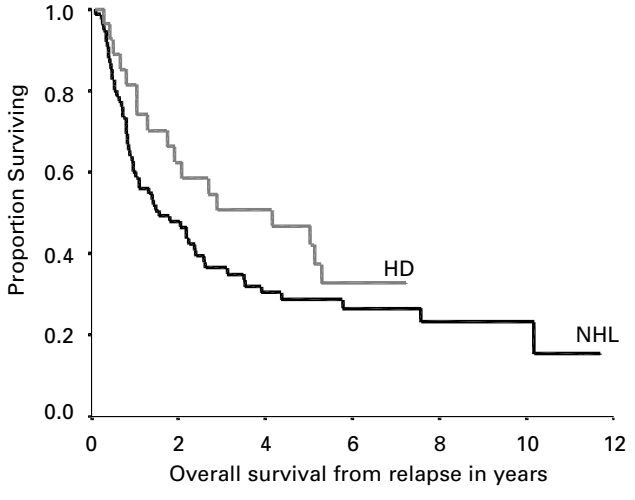

Figure 2 Overall survival from time of relapse/progression post-transplant for those whose disease progressed. The upper curve (grey) represents HD and the lower curve (black) represents NHL. The differences between the curves are not statistically significant ($P = 0.12$) by log-rank test.

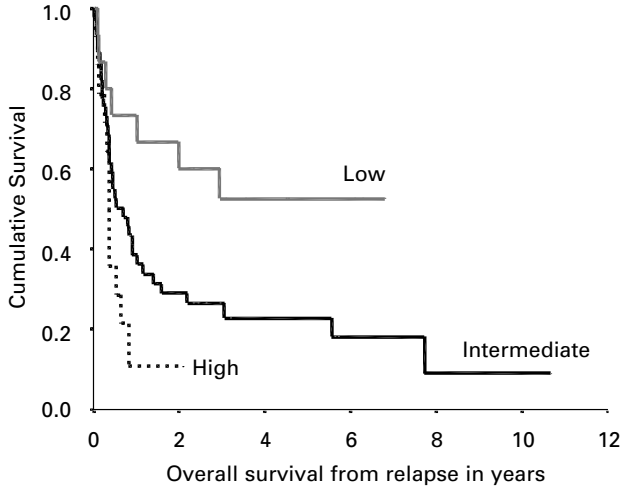

Figure 3 Overall survival for NHL patients from time of relapse/progression post-transplant by histological categories (working formulation). The grey curve represents low-grade histology, the black curve intermediate-grade, and the dotted line high-grade histology. The differences among the curves are statistically significant ($P = 0.007$) by the log-rank test.

Table 3 Multivariate model of prognostic factors for survival in patients whose disease progressed

Factor	*Hazard ratio (95% confidence interval)*	*P-value*
(a) Hodgkin's disease		
Prophylactic immunotherapy	0.29 (0.082–1.04)	0.057
Attained remission	0.22 (0.079–0.63)	0.005
(b) Non-Hodgkin's lymphoma		
Time from transplant to relapse $\geqslant 7$ months	0.22 (0.078–0.61)	0.004
LDH > normal	3.10 (1.05–9.21)	0.042
Attained remission	0.050 (0.02–0.14)	<0.0001

therapy (52% of relapsed HD and 61% of relapsed NHL). Four patients with HD and five with NHL underwent a second transplant (one second autologous and the rest allogeneic). All but two patients with second transplants died from transplant-related complications or refractory disease. One surviving patient with secondary myelodysplastic syndrome in transformation as well as active relapsed NHL remained in remission over 3 years after a nonmyeloablative allogeneic transplant and died after 4 years, from acute myeloid leukemia. The second underwent a nonmyeloablative allogeneic transplant for secondary NHL following HD and is in remission 34 months after the second transplant.[12]

The following potential prognostic factors were included in a multivariate model for survival in patients relapsed post-transplant: age, sex, histology (by Working Formulation grade), LDH at the time of transplant, remission status at the time of transplant, number of previous chemotherapy regimens, time from transplant to relapse, site of relapse, and attainment of postrelapse remission. Table 3 shows the multivariate Cox analyses for HD and NHL separately. In the final multivariate model prophylactic immunotherapy had a borderline ($P=0.057$) association with survival, while attainment of remission was highly associated with survival ($P=0.005$) in HD. For NHL, the factors associated with survival in the multivariate model included time from transplant to relapse (dichotomized according to the median time to relapse ($<$ or $\geqslant 7$ months) ($P=0.004$)), LDH above the upper limit of normal at the time of transplant ($P=0.04$) and attainment of remission ($P<0.0001$).

Although the median survivals for relapsing patients were short, particularly for patients with NHL, it is noteworthy that 17 patients (seven with HD and 10 with NHL) were relatively long-term survivors, who lived >4 years after their post-transplant relapse. There were no long-term survivors among NHL patients with high-grade disease, whereas five patients each (33 and 11%) with low- and intermediate-grade histologies survived for more than 4 years postrelapse ($P=0.02$).

Discussion

The long-term prognosis of patients with NHL and HD whose disease had progressed after high-dose chemotherapy and transplantation was not statistically different in our series. The immediate mortality postrelapse was high for NHL, with 50% of relapsed patients dying within 7.5 months. A small subset of patients survived more than 4 years after relapse, confirming the impression that some patients who have failed high-dose therapy will have an indolent course. No single salvage regimen was found to be superior. Post-transplant prophylactic immunotherapy, which has been shown to delay and prevent relapse[11] may contribute to prolonged survival postrelapse in cases of HD. This possible immunomodulatory effect on post-relapse survival has not been previously shown and requires confirmation in other studies.

In both types of lymphoma, the ability to achieve a remission after relapse was strongly predictive of survival. The observational retrospective design of this study limits our ability to interpret this result. We can only speculate whether this finding is due to patient factors (such as better performance status, blood counts, etc), which enabled retreatment, disease factors (continued responsiveness despite previous high-dose treatment), or due to physician factors (a more aggressive approach, including a willingness to use previously untried therapies). The use of non-BCNU-containing regimens in most patients at this center may have facilitated retreatment with chemotherapy.

For NHL, histology appears to be a prognostic factor, with no long-term survivors found among relapsers with very aggressive (high-grade) histology. Bolwell *et al*[13] have reported that patients with highly aggressive lymphomas who survive the 2-year mark after ASCT are unlikely to relapse; the converse appears to be that patients with these subtypes of NHL who relapse after ASCT are unlikely to survive. The pretransplant LDH level was a predictor of survival postrelapse in NHL patients. LDH has been previously shown to be an important prognostic factor at diagnosis[14] as well as a useful marker at the time of transplant for predicting relapse.[13] The results of our multivariate analysis suggest that the pretransplant LDH level reflects an aspect of tumor biology, which is independent of responsiveness to treatment.

The only other comprehensive study published which reported survival in lymphoma patients who progressed post-ASCT was the Nebraska experience reported by Vose *et al*.[15] They found that median survival postrelapse was 11.5 months for HD and 3 months for NHL, whereas survival in our patients was over twice as long. A smaller study[16] showed a median survival of 11 months for HD patients who relapsed post-transplant. A third study,[17] which described 27 relapsed patients with HD, did not report the overall median survival for all relapsed patients: the authors reported no survival for those with early post-transplant progression and 25% survival for those who relapsed $\geqslant 7$ months after transplant. The longer survival observed in our series may reflect use of more effective salvage regimens, or better performance status among relapsed patients permitting a more aggressive approach to salvage therapy on the part of the physicians. It is also possible that patients in the previous series were more heavily pretreated before their transplant than ours. In the Nebraska series, which included 169 relapsed patients,[13] the difference in survival between HD and NHL patients who

relapsed was statistically significant ($P = 0.0036$), but the profile of the survival functions was very similar to that seen in our patient population. In their series, post-transplant salvage therapy consisting of involved field radiation was associated with a survival advantage, presumably because it reflected localized relapse. As in our series, second transplants were associated with very high mortality rates, and the interval between transplant and relapse was predictive of survival postrelapse/progression.

A more recent study of survival of patients with follicular lymphoma[18] whose disease recurred following autologous transplant reported a median time to relapse of 14 months (compared to 11 months in our series). The median survival for this group after recurrence was approximately 2.5 years compared to a mean survival of 4 years (95% CI: 2.5–5.6 years in our series). The authors compared survival from diagnosis of this patient series with a control group with the same disease histology who had not undergone high-dose therapy and found no difference. The authors raised the question of whether high-dose therapy modifies the natural history of indolent lymphomas, since survival from diagnosis in this patient series did not differ from that in a control group with the same histology who had not undergone ASCT. This issue has also been explored in chronic myelogenous leukemia.[19]

Although every effort was made to obtain complete data including disease status of the patients, our study may have been limited by insufficient power to detect a difference in postrelapse survival between HD and NHL patients. Nonetheless, we have shown that relapsed patients may survive more than a few months after transplant and many can respond and even obtain remission with post-transplant therapy. Given these results, there is an ever-increasing need to perform clinical trials of newer chemotherapeutic and immunologic therapies and transplants following low-intensity conditioning in this expanding group of patients whose lymphoma has progressed despite high-dose therapies.

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