

## ORIGINAL ARTICLE

# Allogeneic SCT for relapsed composite and transformed lymphoma using related and unrelated donors: long-term results

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**Outcome is poor with conventional therapy for relapsed transformed non-Hodgkin's lymphoma (NHL). Autologous SCT has been successfully employed; however the impact of allogeneic SCT has not been well defined. We therefore studied 40 consecutive patients who received allogeneic SCT for relapsed composite and transformed NHL (25 transformed, 8 composite (same site) and 7 discordant (different sites)) with related ( $n=25$ ) and unrelated donors ( $n=15$ ) to evaluate long-term outcome. Conditioning was myeloablative in the majority (39 of 40). Of 40 patients, 11 survive with median follow-up of 25 months. Death occurred in similar proportions due to relapsed NHL ( $n=14$ ) or treatment-related complications (transplant-related mortality, TRM;  $n=15$ ). The cumulative incidence of TRM was 36% at 3 years and disease relapse was 42% at 5 years. Probability of 2- and 5-year event-free survival is 36 and 23% with overall survival 39 and 23%. Performance of SCT within 1 year of NHL diagnosis predicted improved outcome. Relapse and TRM remain significant problems in this setting, indicating the need for strategies whereby patients at high risk of transformation should be selected for early SCT, ideally before their actual transformation.**

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## Introduction

Transformed non-Hodgkin's lymphoma (TNHL) has a poor outcome with conventional therapies. Median overall survival (OS) is 11–22 months for TNHL compared to 77–130 months for non-transformed follicular lymphoma (FL).<sup>1–4</sup> FL transforms into a higher-grade NHL at a rate of 3% per year.<sup>5,6</sup> No randomized clinical trials have been published comparing various chemotherapy regimens for the management of TNHL. Extrapolating from treatment results for *de novo* diffuse large B-cell lymphoma (DLBCL) with CHOP (CY, doxorubicin, vincristine and prednisone) plus rituximab,<sup>7</sup> many physicians consider standard management for TNHL to be CHOP plus rituximab. Following recurrence, response to salvage therapy including radioimmunotherapy is brief with median event-free survival (EFS) of 12 months.<sup>8,9</sup>

Investigators have therefore tried more intensive regimens in an effort to improve results especially in those patients who either do not respond well to primary treatment or relapse soon thereafter. The role of autologous SCT (auto-SCT) has been previously described.<sup>10–13</sup>

There is however scarce literature regarding allogeneic SCT (allo-SCT) for TNHL. It is difficult to assess the true effect of allo-SCT in TNHL as the number of reported patients is small and they are predominantly described in combination with either low- or intermediate-grade NHL patients.<sup>14–16</sup> Furthermore, there are no reported studies regarding the use of unrelated donor stem cell source in TNHL in the myeloablative setting. Nonmyeloablative allo-SCT (NST) for TNHL has resulted in poor disease control and survival.<sup>17</sup> In DLBCL, published studies have demonstrated OS rates between 30 and 50% following allo-SCT with a reduction in relapse rates when compared to auto-SCT patients.<sup>14,16,18,19</sup> Allogeneic transplantation for FL, although associated with a higher transplant-related mortality (TRM) than auto-SCT, has resulted in long-term disease-free survival, plateau in survival curves suggesting cure and significantly decreased relapse rate.<sup>20–23</sup> These data would suggest that allo-SCT may be a useful therapeutic modality for TNHL.

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In this study we report results for 40 patients who proceeded to consecutive allo-SCT with relapsed composite or transformed NHL, 15 with unrelated and 25 with related donors. The role of allo-SCT is evaluated for this disease including investigation for prognostic factors that may influence long-term outcome with this treatment.

## Patients and methods

### Patients

All patients diagnosed with composite or transformed lymphoma who proceeded to high-dose therapy and allo-SCT at the Leukemia/BMT Program of BC between January 1989 and June 2005 were identified. The computerized BC Cancer Agency Lymphoid Cancer and Leukemia/BMT Databases were searched. Data have been prospectively entered into both databases since the early 1980s. Follow-up is complete for all surviving patients to April 2006.

Two groups of patients were identified. The first group (composite lymphoma) included those who had histological evidence of both low- and intermediate-grade lymphoma at diagnosis either at the same anatomical site (composite lymphoma) or at separate anatomical sites (discordant lymphoma), and the second those who following an initial diagnosis of indolent lymphoma had their NHL transform into higher-grade lymphoma (transformed lymphoma). Transformation to higher-grade lymphoma was demonstrated either histologically or clinically. Clinical transformation was defined by presence of any one of the following: rapid localized nodal growth, sudden rise in lactate dehydrogenase ( $\geq 2$  times baseline), unusual extranodal involvement such as liver or bone or hypercalcemia.<sup>5,6</sup> The pathological classification was reviewed by experienced hematopathologists specialized in lymphoid neoplasms (RDG and MC) and has been updated according to the terminology of the current WHO classification.<sup>24</sup>

Stage was assigned according to the Ann Arbor staging system.<sup>25</sup> All patients were assigned a score using the International Prognostic Index (IPI) for DLCL.<sup>26</sup> The Eastern Cooperative Oncology Group (ECOG) scale was used to assess performance status at initial diagnosis of lymphoma.

Patients were treated in a uniform manner based on diagnosis and disease stage according to sequential BC Cancer Agency Lymphoma Group and Leukemia/BMT Program of BC protocols and policies. All patients provided written informed consent, and were treated on protocols approved by the institutional review board. Patients with low-grade lymphoma were generally initially treated with single agent alkylators such as chlorambucil or CY or CVP protocol (CY, vincristine and prednisone).<sup>27</sup> In the 1990s patients with advanced-stage FL were enrolled into two consecutive studies.<sup>28</sup> Patients with intermediate-grade lymphoma (composite/discordant and transformed) were treated with CHOP or CHOP-like regimens<sup>29</sup> with or without rituximab. All patients diagnosed with composite or discordant lymphoma or who transformed into higher-grade lymphoma after March 2001 received rituximab with CHOP chemotherapy.<sup>30</sup> Most patients received salvage

chemotherapy before SCT. Disease response was assigned as per the International Workshop to Standardize Response Criteria for NHL.<sup>31</sup> Clinicopathological characteristics of all patients at the time of initial diagnosis and transformation are summarized in Table 1.

### Transplant details

The median age at SCT was 44 years (range: 28–57) (Table 2). Median interval from diagnosis of NHL to SCT was 26 months (range: 2–204 months). The following conditioning regimens were used for myeloablative allo-SCT ( $n=39$ ). A total of 33 patients (83%) received high-dose CY (50 mg per kg per day for 3 days) and fractionated TBI 1200 cGy (200 cGy twice daily for 3 days) (Cy-TBI-1200). Four patients (10%) received etoposide (1800 or 1200 mg/m<sup>2</sup>, two patients each), high-dose CY (50 mg per kg per day for 3 days) and fractionated TBI at a cumulative dose of 1000 or 1200 cGy (two patients each) (VP16 + Cy + TBI). Two patients (5%) received conditioning chemotherapy alone due to dose-limiting prior irradiation; oral BU (3 mg per kg per day for 4 days) and i.v. CY (90 mg per kg per day for 1 day). One patient was treated with an NST regimen.

The stem cell source consisted of BM in the majority of cases ( $n=27$ , 67%) with peripheral blood (PB) in 13 patients (33%), reflecting standard practice during sequential years.

### GVHD prophylaxis and grading

Prophylaxis for acute GVHD in patients treated with myeloablative allo-SCT consisted of CYA and MTX. CYA was administered intravenously at a dose of 3 mg per kg per day starting 48 h prior to SCT. Oral CSP (6 mg per kg per day) was substituted for the intravenous administration when tolerable. Planned MTX dosing was 15 mg/m<sup>2</sup> on day 1 and 10 mg/m<sup>2</sup> on days 3, 6 and 11.<sup>32</sup> Prophylaxis for acute GVHD in one patient treated with NST consisted of the same dose and regimen of CSP and a reduced dose of MTX at 5 mg/m<sup>2</sup> on days 1, 3 and 6. Acute and chronic GVHD were graded and staged according to a consensus conference on acute GVHD grading<sup>33</sup> and clinicopathological classification of chronic GVHD.<sup>34</sup>

### Statistical methods

Primary end points included OS, EFS, TRM, GVHD and refractory/relapsed disease. Survival curves were constructed according to the Kaplan–Meier method and compared using the log-rank test.<sup>35</sup> Differences were considered significant if the  $P$ -value was  $\leq 0.05$  (two-tailed test). Cumulative incidence curves were prepared where appropriate to account for competing risks such as TRM, GVHD and relapse.<sup>36</sup> GVHD was considered as a time-dependent covariate. Multivariate analysis (MVA) of OS and EFS using Cox proportional hazards models, and methods suitable for evaluating competing risks of GVHD were used as applicable to determine the prognostic significance of pre- and post-SCT factors.<sup>37</sup> Factors that were statistically significant ( $P \leq 0.05$ ) or marginally statistically significant ( $P < 0.35$  and  $> 0.05$ ) on univariate analysis (UVA) and factors that have been previously

**Table 1** Patient clinicopathological characteristics at the time of initial diagnosis of NHL ( $n = 40$ ) and transformation ( $n = 25$ )

Parameter	n (%)	P-value <sup>a</sup>				
		OS	EFS	TRM	Rel	cGVHD
Age, median/range (years) <sup>b</sup>	39/27–55					
Gender, male/female (ratio)	26/13 (67/33); 2:1	0.07	0.12	0.16	0.51	0.71
<i>Diagnosis</i>		0.16	0.21	0.84	0.15	0.95
Transformed lymphoma	25 (63)					
Discordant lymphoma	7 (17)					
Composite lymphoma	8 (20)					
<i>Stage<sup>b</sup></i>						
I/II	2/2 (5/5)					
III/IV	6/30 (15/75)					
Symptoms <sup>b</sup>	11 (28)	0.41	0.51	0.98	0.36	0.33
<i>Stage group<sup>b</sup></i>						
Limited/advanced	3/37 (8/92)	0.76	0.96	0.97	0.98	0.57
BM involvement with NHL	29 (73)	0.68	0.50	0.24	0.36	0.90
ECOG performance status <sup>b</sup>		0.79	0.91	0.88	0.83	0.45
0/1	17/21 (43/53)					
2/3/4	1/1/0 (2/2/0)					
IPI (number of factors) (0–1 vs 2–5) <sup>b</sup>		0.61	0.82	0.43	0.69	0.45
0/1	4/14 (10/35)					
2/3	15/6 (38/15)					
4/5	1/0 (2/0)					
Response to primary treatment		0.43	0.37	0.40	0.74	0.79
CR/PR/PD/ND	13/23/2/2 (33/57/5/5)					
<i>Transformed lymphoma (n = 25)</i>						
Age (median/range)	44/29–55 years					
Gender (male/female)	20/5 (80/20)					
<i>Histology prior to transformation</i>						
FL/SLL/MZL/NS	21/1/2/1 (84/4/8/4)					
Time to transformation (median/range)	18/5–196 months					
Histological/clinical criteria for TNHL	16/9 (64/36)					

Abbreviations: ECOG = Eastern Cooperative Oncology Group; PD = progressive disease; ND = not documented; FL = follicular lymphoma; cGVHD = chronic graft-versus-host disease; IPI = International Prognostic Index; NHL = non-Hodgkin's lymphoma; OS = overall survival; SLL = small lymphocytic lymphoma; MZL = marginal zone lymphoma; TNHL = transformed non-Hodgkin's lymphoma.

<sup>a</sup>P-values based on univariate analysis.

<sup>b</sup>At initial NHL diagnosis of the whole group ( $n = 40$ ).

described as significant in allo-SCT in other types of NHL were included in the MVA models. All survival analyses were performed using S-Plus (version 7.0)/R (version 2.2.1) software for Windows.

The following data were considered for analysis: presenting findings, gender, pathological diagnosis, date of diagnosis, IPI score, tumor size, stage, ECOG performance status at initial diagnosis, treatment before SCT including rituximab and purine analogues, number of treatment cycles before SCT, time between initial diagnosis and SCT, age at SCT, year of transplant, chemosensitivity to salvage chemotherapy, type of the donor: related vs unrelated, conditioning regimen, GVHD prophylaxis, stem cell dose, source of stem cells (PB vs BM), CMV serostatus of donors and recipients, complications of SCT including acute and chronic GVHD, date of last follow-up and if deceased, cause of death.

## Results

### Survival analyses

Of 40 patients, 11 (28%) are alive and free of disease at a median follow-up of 25 months (range 11–74 months). Median duration of OS from SCT is 11 months for all

patients. Two- and five-year probabilities of OS are 39% (95% confidence interval (CI): 26–57%) and 23% (95% CI: 10–49%), respectively. The median duration of EFS from SCT is 8 months for all patients. Two- and five-year probabilities of EFS are 36% (95% CI: 24–55%) and 23% (95% CI: 11–46%), respectively (Figure 1).

No significant predictive factors for OS or EFS were identified in UVA. MVA revealed two significant predictive factors for OS. Development of acute GVHD grades 2–4 ( $n = 23$ ) was associated with a 2.5-fold increased risk of death when compared to the presence of grade 1 or no acute GVHD ( $n = 16$ ;  $P = 0.012$ , hazards ratio (HR) = 2.5). Patients who proceeded to SCT more than 1 year following initial NHL diagnosis ( $n = 32$ ) had four times the increased risk of death compared with those who had their SCT procedure within 1 year of diagnosis ( $n = 8$ ;  $P = 0.021$ , HR = 4.7).

Acute GVHD grades 2–4 ( $n = 23$ ) was also a poor risk factor seen with EFS, increasing the risk of failure by 1.7 in MVA, compared to those patients who developed grade 1 or did not develop acute GVHD ( $n = 16$ ;  $P = 0.042$ , HR = 1.7).

Fifteen patients (38%) received stem cells from unrelated donors (12 matched and 3 with 1AgMM) and six of these fifteen patients (40%) are still alive including 1 of 3 patients

**Table 2** Patient characteristics at the time of transplantation ( $n=40$ )

Parameter	Number (%)	P-value*				
		OS	EFS	TRM	Rel	cGVHD
Age (years) Median/range	44/28–57 years (>46 years)	0.29	0.35	0.02	0.30	0.50
Number of prior therapies						
Median/range	3/1–4					
3 or more regimens	23 (67)	0.14	0.19	0.07	0.68	0.55
Interval from initial NHL diagnosis to SCT (months)						
Median/Range	26/2–204					
<1 year from diagnosis	8 (21)	0.17	0.46	0.21	0.84	0.97
Prior therapy						
CHOP or CHOP-like	33 (83)	0.55	0.38	0.23	0.92	0.77
Purine analogue	17 (43)	0.36	0.21	0.39	0.37	0.74
Rituximab therapy	12 (30)	0.41	0.23	0.75	0.06	0.54
BPVACOP	6 (15)					
Irradiation	13 (33)	0.97	0.80	0.76	0.66	0.24
Source of stem cells (PB/BM)	13/27 (33/67)	0.36	0.26	0.36	0.50	0.67
Stem cell dose (MNCs) ( $\times 10^8$ per kg)						
Median/range	3.5/0.38–15					
< $3 \times 10^8$ per kg	15 (38)	0.89	0.77	0.72	0.45	0.05
Conditioning regimen						
CY + TBI (1200)	33 (83)					
VP16 + CY + TBI	4 (10)					
BUCY	2 (5)					
Flud + CY	1 (2) (NST)					
Donor type, HLA (MS/UD) <sup>a</sup>	25/15 (62/38)	0.75	0.51	0.66	0.22	0.50
Unrelated recipient/donor antigen matching						
HLA-matched	12 (80)					
1 Ag mismatched, HLA-A/-B	1/2 (20)					
CMV serology status		0.78	0.70	0.72	0.98	0.63
Recipient/donor (-/-)	13 (33)					
Recipient/donor (-/+)	4 (10)					
Recipient/donor (+/-)	11 (27)					
Recipient/donor (+/+)	12 (30)					
Chemosensitivity <sup>b</sup> (yes/no)	32/8 (80/20)	0.70	0.68	0.29	0.33	0.73

Abbreviations: BPVACOP = bleomycin, cisplatin, etoposide, doxorubicin, cyclophosphamide, vincristine and prednisone; cGVHD = chronic graft-versus-host disease; MNCs = mononuclear cells; NST = nonmyeloablative stem cell transplant; OS = overall survival; PB = peripheral blood; VP16 = etoposide.

\*P-values based on univariate analysis.

<sup>a</sup>MS/UD: matched sibling/unrelated donor.

<sup>b</sup>Chemosensitivity at the time of SCT was defined as complete (CR = 24) or partial remission (PR = 8) following the most recent chemotherapy.

who received 1AgMM (HLA-A mismatch) SCT. The remainder (9 of 15) died due to GVHD ( $n=5$ ), relapsed lymphoma ( $n=3$ ) and sepsis ( $n=1$ ). Three-year OS and EFS were similar for the related and unrelated groups at 30 and 44% ( $P=0.7$ ) and 24 and 36% ( $P=0.5$ ), respectively. No significant differences in survival (OS, EFS), TRM or relapse were found comparing the transformed lymphoma group ( $n=25$ ) with the composite lymphoma group ( $n=15$ ) ( $P=0.16$ , 0.21, 0.84 and 0.15, respectively). The cumulative 3-year OS and EFS for patients with transformed NHL and discordant or composite NHL were 32 and 25%; 48 and 35%, respectively ( $P=0.16$  and 0.21). Year of SCT was not predictive for OS or EFS. Fifteen, nine, six and three patients survive at periods of greater than 1, 2, 3 and 5 years post-SCT, respectively.

#### Transplant-related mortality

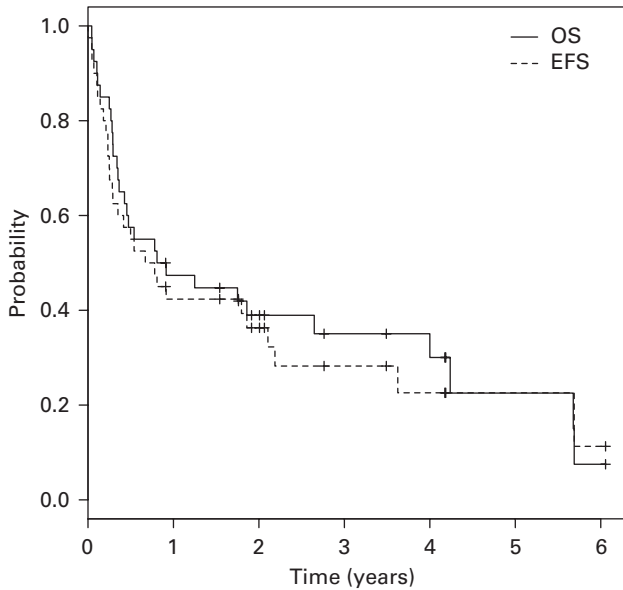
Of 40 patients, 15 (38%) died due to complications related to SCT. Causes of TRM included GVHD ( $n=7$ ), infection ( $n=6$ ), veno-occlusive disease ( $n=1$ ) and atherosclerotic

heart disease ( $n=1$ ). These deaths occurred at a median of 91 days (range: 16–2078 days) post-SCT.

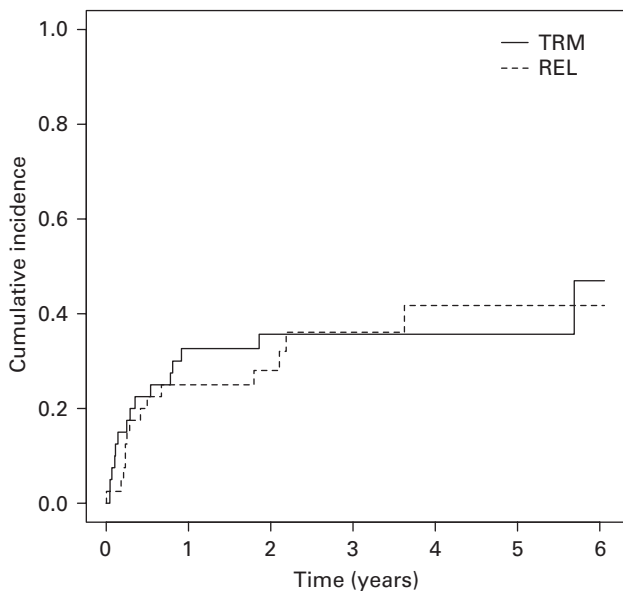
The cumulative incidence of TRM at 1 and 3 years was 33% (95% CI: 18–48%) and 36% (20–51%) (Figure 2). Patients older than 46 years at the time of SCT ( $n=12$ ) had a significantly higher cumulative incidence of TRM at 2 years (61%) compared to those aged  $\leq 46$  years (25%) in MVA ( $P=0.03$ , HR = 1.7). Development of acute GVHD grade 2–4 ( $n=23$ ) was associated with higher risk of TRM compared with grade 0 or 1 GVHD ( $n=13$ ) in MVA ( $P=0.04$ , HR = 1.4). Development of chronic GVHD was associated with increased risk of TRM in MVA ( $P=0.0003$ , HR = 3.8). No significant difference in TRM was seen between patients receiving related or unrelated donor stem cells. TRM did not differ significantly by year of SCT.

#### Progressive lymphoma

Of 40 patients, 14 (35%) with composite or transformed lymphoma developed relapsed NHL at a median of 128



**Figure 1** Probability of overall survival (OS) and event-free survival (EFS) following allo-SCT in relapsed composite and transformed lymphoma ( $n = 40$ ).



**Figure 2** Cumulative incidence of transplant-related mortality (TRM) and relapse following allo-SCT in relapsed composite and transformed lymphoma ( $n = 40$ ).

days (range: 15–1324 days) following allo-SCT. All of these patients subsequently died due to lymphoma at a median of 100 days (range: 13–892 days) post-relapse and 173 days (range 98–2074 days) post-SCT. Five patients received donor lymphocyte infusions (DLI) from matched related donors with no significant improvement noted in disease status. Median time from DLI infusion to death was 176 days (range 33–616 days). The clinical details of all relapsed patients are summarized in Table 3.

The cumulative incidence of relapsed lymphoma at 1 and 5 years was 25% (95% CI: 11–39%) and 42% (23–61%), respectively (Figure 2). Relapse risk did not significantly differ between patients who received related or unrelated

SCT. No significant impact of acute or chronic GVHD was seen with regard to relapse risk.

### GVHD

GVHD contributed to death in 7 of 15 patients who died with transplant-related complications (five with acute GVHD, two with chronic GVHD). Total 23 patients developed acute GVHD grades II–IV with a cumulative incidence of 58% at day 100 (95% CI: 42–73%). The median onset of acute GVHD post-SCT was 19 days (range: 6–43). Total 31 patients lived more than 100 days after SCT and 19 of these 31 patients developed chronic GVHD (14 quiescent, 4 *de novo*, 1 progressive). The cumulative incidence of chronic GVHD was 45% at 1-year post-SCT (95% CI: 29–61%). The median onset of chronic GVHD was 111 days post-SCT (range: 100–185). Characteristics of acute and chronic GVHD are summarized in Table 4. As per the above, both acute and chronic GVHD were noted to have a negative impact on OS, EFS and TRM, with no significantly positive impact upon relapse risk.

Patients who received a mononuclear cell (MNC) dose  $< 3 \times 10^8$  per kg ( $n = 13$ ) had an increased risk of developing chronic GVHD by 60% compared with those who received  $\geq 3 \times 10^8$  per kg MNC ( $n = 18$ ) ( $P = 0.05$ , HR = 0.4). Stem cell dose had no effect on OS, EFS, TRM or disease relapse.

### Discussion

The outcome of patients receiving allo-SCT for relapsed composite or transformed lymphoma is reported in this large, population-based, single-center prospective cohort study with long and complete follow-up. This is the first report to comment on the role of allo-SCT in a large group of such patients. This study is also the first to report on the role of unrelated myeloablative allo-SCT in this disease and shows comparable survival, TRM and relapse probabilities to those treated with matched sibling allo-SCT. However, the relatively small patient numbers in each group render statistical analysis difficult due to the lack of power for detecting a possible difference. Relapse risk is however higher in this population than that seen with myeloablative allografting in indolent NHL, and approaches the relapse risk for chemoresistant aggressive NHL.<sup>16,21,38,39</sup> Moreover, treatment-related mortality for patients in our study appears to be higher than that seen for either indolent or aggressive NHL patients proceeding to myeloablative allograft.<sup>16,38</sup> These data suggest that although allo-SCT may rescue a proportion of patients with transformed and composite lymphoma, more ideal strategies would include use of therapy designed to prevent transformation and early application of allo-SCT to patients with indolent NHL at high risk of transformation.

Several groups have previously reported the use of auto-SCT for relapsed transformed lymphoma. The largest trial to address this issue was reported by Williams *et al.*<sup>12</sup> from the EBMT describing 50 patients with chemosensitive TNHL who underwent auto-SCT. Five-year OS and

**Table 3** Clinical details of 14 patients with composite and transformed lymphoma who relapsed post-allo-SCT

UPN	Age at SC T/gender	Diagnosis	Prior therapy	Conditioning	Type of donor/SC source	Time to relapse (day) <sup>a</sup>	Treatment post-relapse	Time to death (day) <sup>a</sup>
631	37/F	Disc	VACOPB, PRED-ETOP	CY + TBI	UD/BM	656		1548
759	44/M	FL-Tran	BPVACOP-RAD, CHLO-PRED-CY	CY + TBI	RD/BM	66	RAD	156
985	46/M	FL-Tran	CHLO, CHOP	CY + TBI	RD/BM	152		166
1033	33/M	NS-Tran	CPF, CY	BU + CY	UD/BM	85		103
1222	32/F	FL-Tran	BPVACOP-RAD, CHLO-CY-RAD	BU + CY	RD/BM	799	CY-PRED, DLI	967
1225	40/M	FL-Tran	CPF, ACOP	CY + TBI	RD/BM	182	RAD, CHLO	639
1528	30/F	MZL-Tran	RAD- CHLO, RAD, RAD	CY + TBI	RD/BM	245	DLI	456
1634	44/F	FL-Tran	ACOP, ACOP, DHAP	CY + TBI	RD/BM	1324	CHOP-R RAD, CY, DLI	2074
1687	40/M	FL-Tran	CPF	CY + TBI	RD/BM	769	R, CHOP, FLUD, DLI	1461
1810	49/M	FL-Tran	CHLO, FLUD, CHOP, ICE	CY + TBI	RD/BM	104		173
1824	30/M	SLL-Tran	FLUD, CHLO-PRED, CHOP	CY + TBI	RD/BM	92		133
2039	56/M	FL-Tran	FLUD, CHOP, ICE-GDP	FLUD + CY	RD/NST/PB	15	DLI	124
2117	28/M	Disc	CY-MTX	CY + TBI	UD/PB	85		98
2311	44/M	Comp	CHOP-RAD, GDP-R	CY + TBI	RD/PB	77		107

Abbreviations: ACOP = doxorubicin, cyclophosphamide, vincristine and prednisone; BPVACOP = bleomycin, cisplatin, etoposide, doxorubicin, cyclophosphamide, vincristine and prednisone; CHLO = chlorambucil; Comp = composite lymphoma; CPF = cyclophosphamide, prednisone and fludarabine; Disc = discordant lymphoma; DLI = donor lymphocyte infusion; FL = follicular lymphoma; FLUD = fludarabine; GDP = gemcitabine, dexamethasone and cisplatin; ICE = ifosfamide, carboplatin and etoposide; MZL = marginal zone lymphoma; NST = nonmyeloablative SCT; PB = peripheral blood; PRED = prednisone; R = rituximab; RAD = irradiation; RD = related donor; SC = stem cell; SLL = small lymphocytic lymphoma; Tran = transformed lymphoma; UD = unrelated donor; UPN = unique patient number; VACOPB = etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone and bleomycin.

<sup>a</sup>Time from SCT.

**Table 4** Characteristics of GVHD in patients with composite and transformed lymphoma (*n* = 40)

Acute GVHD ( <i>n</i> = 26)	Number (%)
Onset days (median/range)	19/6–43 days
<b>Overall grade</b>	
Grade I	3 (12)
Grade II	13 (50)
Grade III	7 (27)
Grade IV	3 (12)
<b>Chronic GVHD (<i>n</i> = 19 of 31 patients surviving <math>\geq 100</math> days post-SCT)</b>	
Onset days (median/range)	111/100–185 days
<b>Grade</b>	
Limited	3 (16)
Extensive	16 (84)
<b>Type</b>	
Quiescent	14 (74)
Progressive	1 (5)
<i>De novo</i>	4 (21)

Abbreviation: GVHD = graft-versus-host disease.

progression-free survival (PFS) rates were 51 and 30%, respectively, with relapse (50% of patients relapsed) constituting the major cause of treatment failure.<sup>12</sup> Other auto-SCT studies in TNHL by Chen *et al.*<sup>13</sup> and Foran *et al.*<sup>10</sup> described PFS of 36% at 5 years and 52% at 4 years, respectively. Importantly, the incidence of therapy-related myelodysplasia in patients with TNHL treated with auto-SCT is reported to be between 7 and 15%.<sup>10,11,13</sup> This complication has not occurred in our patients; however, longer follow-up is needed to confirm this finding. The high

relapse risk observed following autograft prompted consideration of other therapies that may have higher curative potential. Several previous reports describe a GVL effect following post-allo-SCT in different types of lymphoma,<sup>21,39</sup> however this has not been previously addressed in TNHL. Significant relapse rates and high TRM with allo-SCT in this study suggest that this modality may not result in a better overall outcome for many or most patients with TNHL, and a direct comparison between the two treatment modalities is needed. We did not demonstrate a statistically significant impact of acute or chronic GVHD on the risk of relapse; however, this would likely require larger patient numbers to do so. It remains to be seen whether results with allografting may, with further follow up, be more durable than those seen with autografting. Although a randomized controlled trial would be ideal, it is not highly likely that this will be possible given the relatively small patient numbers, and heterogeneity. Larger cohort comparisons, either multi-institutional or larger single institution may help clarify this issue.

Factors that may be associated with TRM, such as stem cell source (related vs unrelated donor, BM vs PB), CMV serostatus, chemosensitivity and prior chemotherapy were examined in our study and found not to be predictive. In our series older age (>46 years) at the time of transplantation was associated with a higher risk of TRM. A possible strategy to reduce this risk would be to favor use of NST in patients >46 years. However, the role of NST in patients with aggressive histology NHL has been previously reported with conflicting results; TRM ranges between 10 and 40% and relapse rates are between 30 and 70%.<sup>17,40–43</sup>

Moreover, chemoresistant disease has not been adequately controlled in this setting, and both relapse and TRM remain concerns. Tandem auto-SCT/NST may circumvent these issues, but no series have been published to date.

Few reports have examined the role of unrelated SCT in NHL. The largest is from the Japanese BMT registry ( $n = 124$ ),<sup>44</sup> however no patients with TNHL were included in this study. Izutsu *et al.* reported 3-year OS and PFS of 49 and 42%, respectively with a median follow-up duration of 565 days for NHL patients following unrelated donor allografts. In our study, 3-year OS and EFS for patients receiving unrelated myeloablative SCT were not dissimilar at 44 and 36% respectively at a median follow-up of 750 days.

We found that patients who proceeded to allo-SCT within 1 year of the initial diagnosis had significantly better OS compared to those who were transplanted later. The favorable effect of early transplant on risk of relapse in FL has been previously reported.<sup>38</sup> Patients with TNHL in this study have higher rates of both relapse and TRM when compared with otherwise similar patients with advanced FL treated in our institution with similar myeloablative allograft protocols. The cumulative incidence of relapse and TRM in FL patients post-allo-SCT at our institution was 18 and 24%, respectively at 3 years,<sup>38</sup> both lower than for patients in this series. Moreover, when patients who in retrospect met clinical criteria for transformed NHL were removed from our prior analysis, the revised relapse risk for FL was 3% and OS was 66% at 5 years post-allo-SCT (unpublished data, C Toze). These findings suggest that early SCT for patients with high-risk indolent NHL<sup>6</sup> prior to actual transformation may improve outcome via both lower risk for relapse and TRM.

In summary, this is the largest report regarding the application of allo- (including unrelated donor) SCT in patients with relapsed transformed or composite low- and intermediate-grade NHL. Successful use of unrelated donors may afford the benefits of allo-SCT to young patients who lack a suitable family donor. The higher TRM observed in patients older than 46 years would suggest a strategy of auto-SCT followed by NST may reduce both relapse risk and TRM in this population. Both relapse and TRM remain significant problems in this patient population even after myeloablative allo-SCT.

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