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A 15-Year Analysis of Early and Late Autologous Hematopoietic Stem Cell Transplant in Relapsed, Aggressive, Transformed, and Nontransformed Follicular Lymphoma

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ABSTRACT

Autologous stem cell transplant (ASCT) has been shown to be an effective treatment for follicular lymphoma (FL). We explored our experience in ASCT for FL among all patients treated over a 15-year period from diagnosis through their entire treatment history including relapse post ASCT. All patients who underwent an unpurged ASCT for relapsed, advanced FL between June 1990 and December 2000 were analyzed. After salvage therapy they received melphalan/etoposide/total body irradiation, BCNU, etoposide, cytarabine, melphalan (BEAM), or cyclophosphamide/BCNU/etoposide (CBV) as conditioning for the ASCT. One hundred thirty-eight patients with a median age of 48 years and a median follow-up of 7.6 years were analyzed. The majority were of the subtype grade 1, nontransformed (FL-NT), having had 1 prior chemotherapy. The progression-free (PFS) and overall survival (OS) of the FL-NT at 10 years were 46% and 57%, respectively, and at 5 years for the transformed (FL-T) were 25% and 56%, respectively, of which only the PFS was significantly different ($P = .007$). The median OS from diagnosis was 16 years for the FL-NT. ASCT positively altered the trend of shorter remissions with subsequent chemotherapies, and there was no difference in OS between those who had 1, 2, or >2 chemotherapies prior to ASCT. Salvage therapy for relapse post ASCT was effective (OS >1 year) in a third of patients. Unpurged ASCT is an effective tool in the treatment of relapsed, aggressive FL-NT and FL-T, is superior to retreatment with standard chemotherapy, is effective at various stages of treatment, is likely to have a beneficial influence on the natural history of this disease, and the disease is amenable to salvage therapy post-ASCT relapse.

KEY WORDS

Follicular • Lymphoma • Transformed • Relapse • Autologous stem cell transplant • Radiation

INTRODUCTION

Follicular lymphomas (FL) are a group of non-Hodgkin's lymphomas (NHL) with an indolent course [1]. Traditionally, treatment has consisted of chemotherapy and/or radiotherapy, [2] and the overall survival (OS) has been shown to range from 7 to 10 years [3]. Until recently, no therapy has been superior to another, in terms of OS from a "watch and wait" to an intensive combination chemotherapy approach [4-11]. Once treatment is initiated, the first remission lasts 1-3 years and the OS is 4-5 years. Subsequent remissions become shorter with each additional course of treatment [4,12-14]. Finally, in about 20%-30% of patients the lymphoma may transform to a higher grade lymphoma (FL-T) which carries a poorer prognosis [13,15,16].

Autologous stem cell transplants (ASCT), following high doses of chemotherapy and/or radiotherapy, were introduced as a strategy to salvage patients who had relapsed from conventional chemotherapy. Dose intensification has been shown to be effective in many studies in other lymphomas [17-20], illustrating the direct relationship between the dose of a given che-

motherapy and the ultimate response [21]. Several groups have, more recently, reported on their experience with ASCT, generally confirming that ASCT appears to have a positive impact upon the natural history of the disease [22-31].

In phase II studies, ASCT has been demonstrated to be valuable in the relapsed setting producing superior survival outcomes than would be expected from conventional chemotherapy [28,31]. Some of these groups have attempted to use a purged stem cell product, which is negative by the polymerase chain reaction (PCR) at transplant. These groups have shown that there appeared to be a lower risk of relapse in those who were able to be purged, usually with a variety of monoclonal antibodies (mAb), of the marker gene; however, it is not clear if a survival advantage has been demonstrated over an unpurged stem cell product [23,25,28,32].

Attempts have been made to try and apply the successes seen in treating the follicular nontransformed lymphomas (FL-NT) to the more dismal situation where transformation has occurred. In general, they appear to continue to have a poorer outcome as demonstrated by several studies [33-35]. However, a more recent survey by the EBMT suggested that a subset of FL-T patients may benefit from such intensive therapy [36].

Salvage therapy for many diseases for relapse post-ASCT such as in acute leukemia and aggressive lymphoma is traditionally thought of as fruitless as few patients can achieve prolonged remissions. However, there are at least 2 reports examining, primarily, this question in FL. Both indicated that there is a subset of patients in whom salvage therapy is useful producing prolonged remissions [37,38].

In this paper, we describe our large cohort, primarily within a local community of unselected patients with relapsed aggressive FL treated with an unpurged ASCT from diagnosis through the natural history of their disease.

PATIENTS AND METHODS

Patient Groups

This study includes all patients referred to the Ottawa Hospital's Blood and Marrow Transplant Program (TOH-BMT), a regional tertiary care referral center (between June 1990 and December 2000) with relapsed aggressive FL (FL-NT or FL-T) who received an ASCT. All had failed or progressed after at least 1 course of chemotherapy. Follow-up of the patients continued through to the end of December 2005.

Salvage Therapy prior to ASCT

Patients received at least 1 course of salvage chemotherapy with either CHOP, DHAP, or mini-BEAM (BCNU, etoposide, cytarabine, cyclophosphamide). Patients with insufficient disease control (<50% reduction in the initial mass) after at least 2 of these regimens were classified as chemotherapy-insensitive (CIS). Those that responded were classified as chemotherapy-sensitive (CS).

Stem Cell Collection

Stem cells were collected by bone marrow harvest and/or a peripheral blood stem cell (PBSC) collection to achieve a target of 2.5×10^6 $CD34^+$ cells/kg, usually following the second cycle of salvage chemotherapy. Filgrastim (G-CSF [300 μg if <70 kg and 480 μg if >70 kg]) was introduced in the collection regimen after July 1992. It was used for at least 10 days following the second chemotherapy regimen and continued until completion of the stem cell harvest (10-12 days). Prior to June1993 most ASCTs were completed using bone marrow. After March 1994, PBSC collections were almost exclusively used.

Conditioning Regimens

Patients with FL-NT were treated with a combination of etoposide (60 mg/kg i.v. day −2) melphalan (140 mg/m^2 i.v. day −1), and total body irradiation (TBI) (day 0). Patients who were judged to be FL-T, either on rebiopsy or because of a rapid clinical change such as rapidly growing lymph nodes, increasing lactate dehydrogenase, or systemic symptoms that had not been previously present were treated with BEAM, after September 1997 [39,40]. Prior to this date they were treated with CBV.

The dose of TBI used was 1200 cGy in 6 fractions prior to September 1992, and was subsequently changed to 500 cGy in a single fraction Therefore, most patients in the FL-NT group had a lower dose of TBI, as this was reduced early in the cohort to minimize toxicity and none of the FL-T were treated with radiation.

Unpurged bone marrow (BM), PBSC, or both was then reinfused. PBSC were favored over BM in the FL-NT group, as this has become the preferred stem cell product over the past decade [41].

Follow-up

Disease progression was monitored by members of TOH-BMT or the referring hematologist every 3 months with CT scans for the first 2 years and then 2-3 times/year.

Statistics

We evaluated baseline characteristics of the described cohort of patients by computing appropriate measures of frequency, central tendency, and dispersion for risk factors of interest. Baseline characteristics were compared for differences using the chi-square analysis

Table 1. *Patient Characteristics*

Characteristics	FL-NT	FL-T
Subjects	115	23
Median overall age (years) range	48 (22-62)	49.6 (30-65)
Median follow-up of survivors (years) range	7.7 (1.1-13.8)	7.6 (6.1-9.6)
Sex		
Male	71	13
Female	44	10
Subtype		
Grade 1	74	9
Grade 2	36	8
Grade 3	5	4
Undefined	1	1
Median duration of first remission (years) range	1.2 (0-8.2)	0.6 (0-5.8)
Median time from diagnosis to ASCT (years) range	2.8 (0.5-15)	3.6 (0.3-20)
TBI dose (Gy)		
500 cGy/1 fraction	95	0
1200 cGy/6 fractions	20	0
Stem cell source		
PBSC	73	16
BM	22	0
Both	20	7
Number of prior chemotherapies		
1	61	11
2	29	7
>2	25	5

PBSC indicates peripheral blood stem cells; ASCT, autologous stem cell transplant; TBI, total body irradiation; FL-NT, follicular lymphoma—nontransformed; FL-T follicular lymphoma—transformed; BM, bone marrow.

for categoric variables and the Mann-Whitney test for continuous variables. Subsequently, the influence of these risk factors on duration of both progression-free (PFS) and OS in FL-NT patients was evaluated using Kaplan-Meier plots and log-rank statistics to perform univariate assessments, and Cox Proportional hazards modeling to perform multivariable assessments. The collection of risk factors considered in this investigation included the following: age at BMT (≤40 years versus >40 years), sex, number of chemotherapies prior to salvage, and blood and marrow transplantation (BMT) (1, 2, >2), product received (PBSC, marrow, or both), TBI dosage (500 cGy/1 fraction versus 1200 cGy/6 fraction), diagnosis (FL grade 1, 2, 3), chemosensitivity status, duration of time between diagnosis, and BMT (<6 months, 6 months to 1 year, >1 year), and duration of time between final chemotherapy session and BMT (<6 months, 6 months to 1 year, >1 year). A statistical significance level of 5% was chosen for all tests, and 95% confidence intervals were computed for all hazard ratios estimated in the multivariable analysis.

Adverse outcomes such as relapse, deaths, treatment-related mortality (TRM) (ie, all deaths <100 days post-ASCT unrelated to disease progression), secondary malignancies, nonrelapse mortality (NRM) (ie, all deaths unassociated with relapse or TRM), were calculated as absolute percentages.

All statistical analyses were carried out using SAS, version 8.1 (SAS Institute, Cary, NC).

RESULTS

Patient Population

A total of 138 patients, between the ages of 22 to 65 years, had an ASCT between June 1990 and December 2000. The majority of the patients were male and initially diagnosed as follicular grade I. The demographics of this population are shown in Table 1. The median length of follow-up from ASCT was 7.7 years for FL-NT and 7.6 years for FL-T. Because the median duration of the first remission was 1 year, much shorter than the typical 2.5 years, the cohort was described as an "aggressive" FL [13,14,28].

Outcome post-ASCT

Patient outcomes are presented in Table 2. The estimated OS and PFS, as outlined, in Table 3, of the FL-NT at 10 years post-ASCT was 57% and 46%, respectively. The OS and PFS at 5-years for the FL-T was 56% and 25% (Figure 1A and B).

The median OS from diagnosis is 16 and 11 years for the FL-NT and FL-T groups, respectively (Figure 2).

The relapse rate was 37% and 74%, for FL-NT and FL-T, respectively. There was a similar proportion of deaths among the 2 groups (40% and 43%). The NRM was not significantly different between the 2 groups, nor was the TRM. Long-term toxicity in the form of developing either another malignancy or myelodysplasia post transplant was 7% in the FL-NT group and 18% in the FL-T.

Table 2. *Outcomes Post-ASCT*

	FL-NT (%)	FL-T (%)	*P* Value
Adverse events post-ASCT			
Relapse	43 (37)	17 (74)	.002
MDS	5 (4)	2 (9)	NS
Adenocarcinoma/cancer	4 (3)	2 (9)	NS
Mortality post-ASCT			
Total number of deaths	46 (40)	10 (43)	NS
TRM (<100 days)	3 (3)	0 (0)	NS
NRM	16 (14)	1 (4)	NS

TRM indicates treatment-related mortality (i.e., death within 100 days of ASCT that was not resulting from disease progression); MDS, myelodysplasia; NRM, nonrelapse mortality (ie, all deaths not resulting from disease progression or TRM, including those from MDS, malignancy or other [ie, stroke, sepsis, cardiac arrest, pulmonary fibrosis, and suicide]); FL-NT, follicular lymphoma—nontransformed; FL-T, follicular lymphoma—transformed; NS, not significant.

Effect Number of Previous Therapies on Outcome

Among the many therapies that these patients are subjected to along their treatment course, an attempt to elucidate the influence of ASCT was carried out by comparing the interval between therapies. Patients were divided up by the number of standard chemotherapies prior to ASCT (1, 2, or >2), and Kaplan-Meier curves were constructed illustrating the time to next treatment (TTNT) between the chemotherapies and the PFS after ASCT. As shown in Figure 3A-C, a similar trend is seen, most notably that with successive number of standard chemotherapies the remission duration is shorter; however, post-ASCT the PFS was much longer than the previous TTNT. Although we are comparing 2 different measures (TTNT and PFS), the TTNT is generally more prolonged than the PFS, as patients are usually monitored beyond the time that progression of disease is noted to the time that another therapy is indicated; therefore, this analysis should underestimate the difference between disease progression pre- and post-ASCT.

The timing of ASCT has also been debated, some arguing for earlier versus later intervention [42-45]. To attempt to address this issue the PFS from each of these groups (1, 2, >2 prior chemotherapies) was then compared to assess if there was any difference in PFS if ASCT was performed earlier or later in the treatment course. As shown in Figure 4A the PFS from the above analysis is not significantly different. Further the OS between these 3 groups (Figure 4B) is not significantly different either from ASCT (P = .41) or from diagnosis (P = .88, not shown). Therefore, it does not appear that ASCT must be done earlier in the treatment course to be maximally effective.

Outcomes Once Relapsed after ASCT

We finally examined the course of those who relapsed post-ASCT. Among the 43 of 115 (37%) FL-NT and 17 of 23 (74%) FL-T, patients who relapsed post-ASCT the median time from ASCT to relapse was 1.3 and 0.9 years, respectively. This is in keeping with previous observations by others demonstrating a median time to relapse of 11-14 months [37,38]. Salvage therapy post-ASCT was provided to 29 of 43 (67%) FL-NT and 13 of 17 (76%) FL-T patients using any 1 or combinations of the following treatments: Radiation, chemotherapy, rituximab, allogeneic stem cell transplant, node removal, or supportive care. OS and PFS from salvage therapy are illustrated in Figure 5. No single therapy stood out as more beneficial in this setting, including rituximab and allogeneic stem cell transplant. Although more patients who lived longer than 1 year received either rituximab or an allogeneic stem cell transplant compared to those who did not survive >1 year this result was not statistically significant.

Although, there was a significantly greater number of patients in the FL-NT compared to the FL-T

Table 3. *Progression-Free and Overall Survival Outcomes Based on Individual Characteristics*

	OS from ASCT (%)			PFS after ASCT (%)		
	5 Years	10 Years	*P* Value	5 Years	10 Years	*P* Value
FL-NT	72	57	.33	56	46	
FL-T	56			25		.007
FL-NT						
Age (years)						
<40	96	79	.003	77	60	
>40	65	50		52	44	.08
Histology						
Grade 1/2	74	58	.12	59	47	
Grade 3	40			40	40	.3
TBI dose (cGy)						
500 cGy/1 fraction	69	52	.11	56.1	40.4	
1200 cGy/6 fractions	85	75		75	70	.04
Stem cell Source						
BM	82	72	.45	77	68	
PBSC	70	57		58	46	
Both	65	44		45	31	.11
# CT						
1	73	63	.48	63.6	53	
2	75	62		50.1	46	
>2	67	42		59.3	37	.66
Chemosensitivity						
CS	75	59	.01	62	50	
CIS	29	—		14	—	<.0001

OS indicates overall survival; PFS, progression-free survival; FL-NT, follicular lymphoma—nontransformed; FL-T, follicular lymphoma—transformed; TBI, total body irradiation; PBSC, peripheral blood stem cells; CT, chemotherapy; CS, chemosensitive; CIS, chemoinsensitive; ASCT, autologous stem cell transplant; BM, bone marrow.

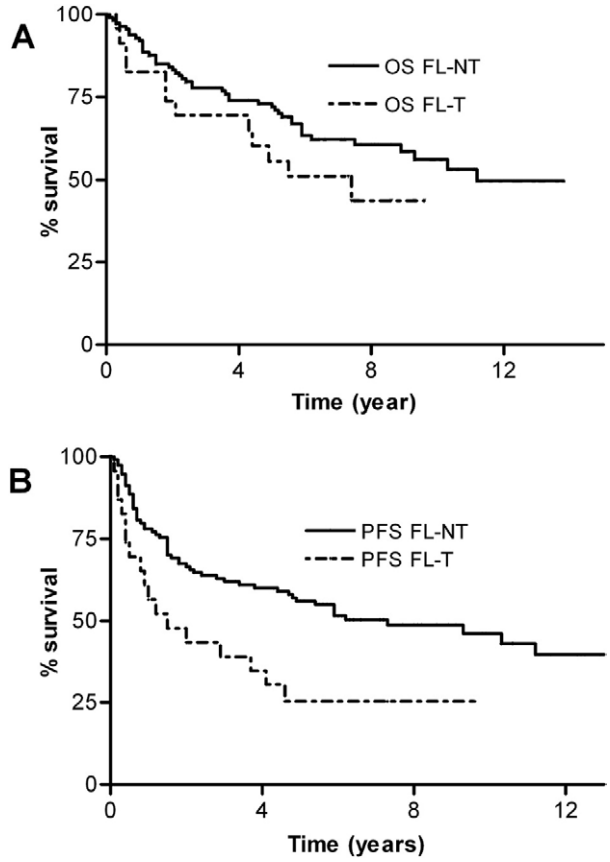

Figure 1. Survival from ASCT between the FL-NT and the FL-T. A, Overall survival (OS) [FL-NT versus FL-T, $P = .33$]; B, Progression-free survival (PFS) [FL-NT versus FL-T, $P = .007$].

group who received chemotherapy over radiation, which might imply that the FL-NT were treated more aggressively, their OS were similar, with approximately 30% achieving a prolonged remission. Presently, 13 FL-NT patients and 5 FL-T patients are alive 1-11 years and 2-7 years, postrelapse after ASCT, respectively.

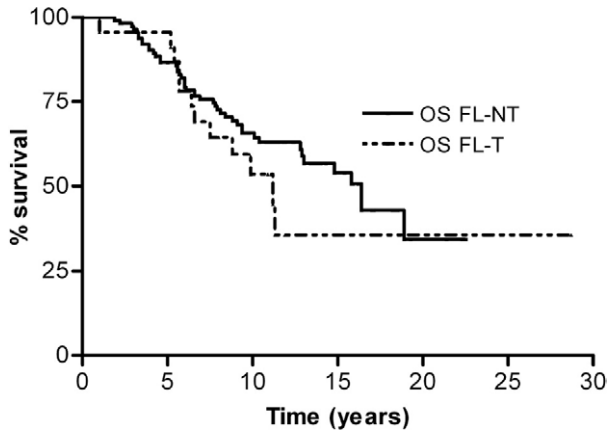

Figure 2. Overall survival (OS) from diagnosis $P = .25$.

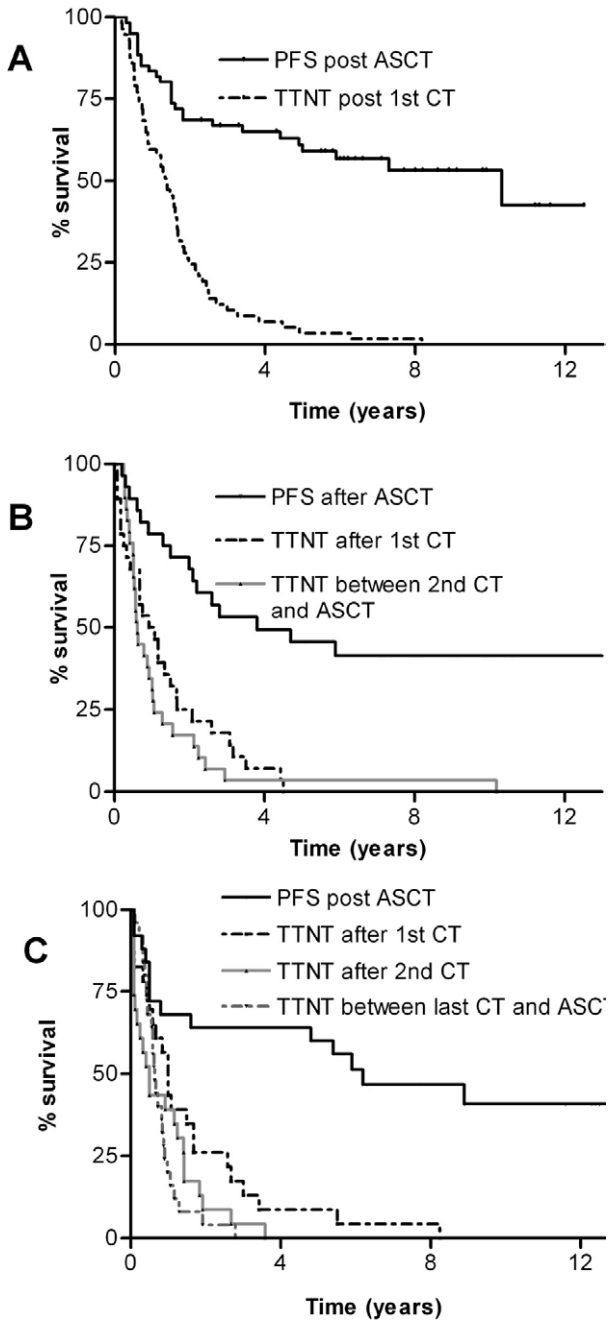

Figure 3. Comparison between the time to next treatment (TTNT) prior to ASCT and PFS post ASCT: A, After 1 chemotherapy (CT); B, after 2 CT; C, after >2 CT.

Prognostic Factors Prior to ASCT Predicting Survival

Univariate and multivariate analyses on survival outcomes were performed for the FL-NT group. Univariate analysis using Kaplan-Meyer plots and log-rank statistics demonstrated that chemosensitivity ($P = .01$) and age <40 ($P = .01$) were positive predictors of survival.

Multivariate analysis cox proportional hazards modeling also identified chemosensitivity ($P < .01$)

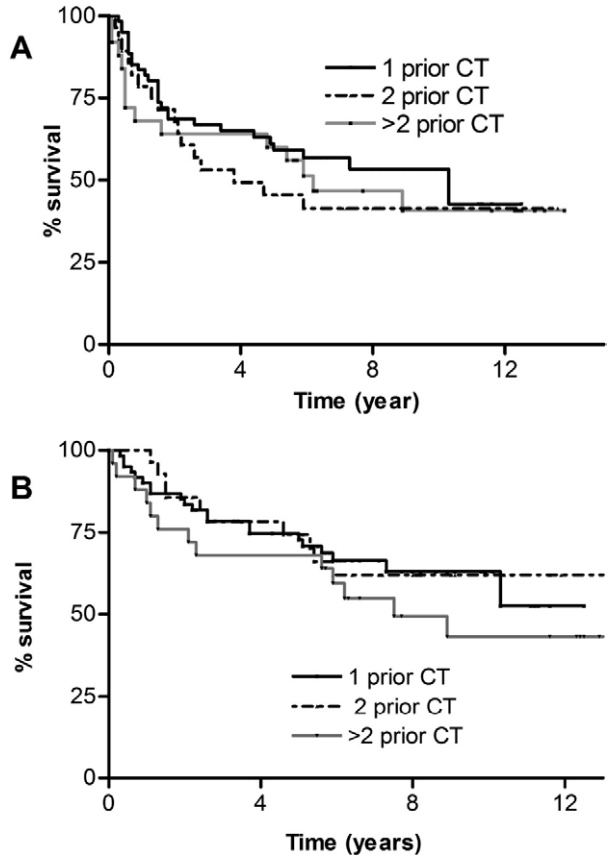

Figure 4. Survival from ASCT based on prior number of chemotherapies (CT). A, progression-free survival. B, Overall survival. Neither is statistically significant.

and age <40 (P = .02) as positive predictors of survival. In addition, when time was taken into account with respect to the TBI survival curves, this interaction term between TBI dosage and time demonstrated a positive effect with higher dose (P = .03), as demonstrated in Figure 6.

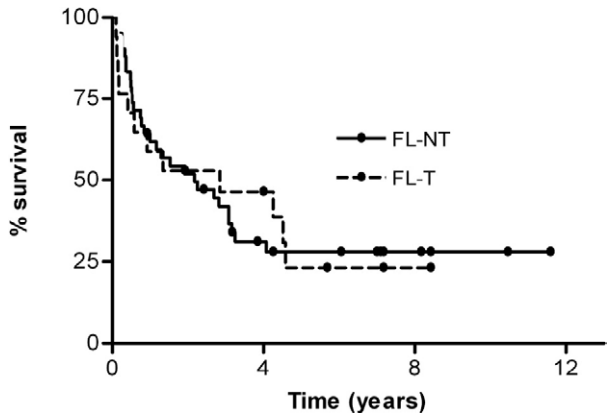

Figure 5. Overall survival from relapse post-ASCT of those who relapsed postASCT.

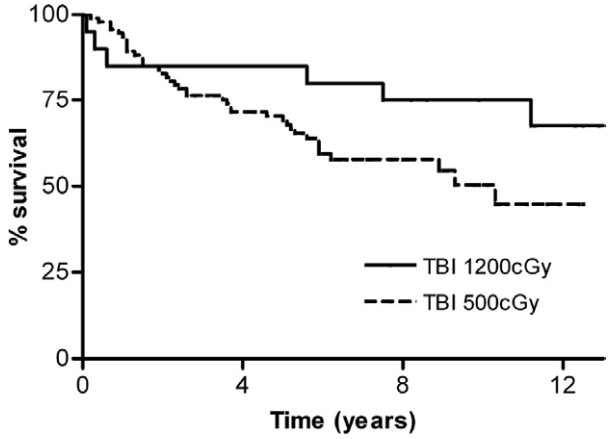

Figure 6. Overall survival comparing dose of TBI (1200 cGy in 6 fractions versus 500 cGy in 1 fraction).

DISCUSSION

ASCT for FL has been investigated by many groups in an attempt to demonstrate its role in the treatment of FL and at what point such a treatment should be introduced [23-25,27,28,30,43]. PFS, in these studies, ranged between 42% and 63%, and OS was estimated to be between 65% and 84% at 4-9 years. However, because of the long natural history of this disease, it has been difficult to present consistent convincing evidence that ASCT has had an impact on survival outcomes.

Our analysis of a 15-year follow-up of a cohort of patients with "an aggressive," relapsed FL after being treated with an unpurged ASCT using a uniform conditioning regimen further adds strength to the argument that ASCT is an effective therapy for relapsed FL. Through this cohort we have evidence that the natural history has had an impact on such intensive therapy in terms of the median survival from diagnosis, which is 16 years, longer than the 7-10 years reported with conventional therapy. This trend is also supported by results from others such as Freedman's group who reported an OS of 69% at 12 years from diagnosis [28].

The stubbornness of this disease to remain in remission after most therapies has been well documented, and that once relapse has occurred subsequent remissions tend to be shorter than the previous one. We demonstrate here that this trend does not seem to apply to ASCT, and that there was no difference in OS among those who had 1, 2, or >2 prior chemotherapies (Figures 3 and 4B), either from ASCT or from diagnosis [14,24,31]. Therefore, it appears as though ASCT can overcome some of the refractoriness of the disease, without losing too much effectiveness with later relapses, contrary to previous publications [43,46,47].

This cohort also highlights that those patients with an FL-T, although considered quite refractory to

treatment may benefit from ASCT and are certainly not hindered from pursuing alternate therapies at relapse. As discussed below, the nature of the disease may be different at relapse and more amenable to therapy at that point.

In this study the only factors analyzed by a multivariate analysis that were significant were age, chemosensitivity, and a higher TBI dose with time.

The impact of TBI is interesting because although it is known to be effective in lymphoma, it is feared because of its potential for causing long-term toxicity in the form of secondary malignancies and myelodysplastic syndromes (MDS) [48,49]. This issue was reviewed by the International Bone Marrow Transplant Registry (IBMTR) and European Bone Marrow Transplantation Registry (EBMTR), who indicated that despite its effectiveness in controlling lymphoma, it resulted in an increased TRM [32,36]. In contrast, our analysis of our cohort suggests that the early toxicity as seen in Figure 6 does not obscure the superior long-term survival of the higher dose of radiation. However, it should be noted that differences between these 2 groups did exist, most of which were accounted for in the multivariate analysis except for year of transplant, which is the most obvious difference between the 2 groups as all the high dose TBI was done within the first 2 years of the cohort. Interestingly, radiolabeled antibodies have begun to be used in this setting and have demonstrated a decreased TRM while preserving its effectiveness, so that this modality may become the preferred way of delivering this part of the treatment [50]. Therefore, despite the competing risks, it appears that the benefits of radiotherapy outweigh the long-term risks but this will have to be addressed in future studies.

Salvage therapy of relapse post-ASCT has been previously analyzed over the past decade [37,38]. Rates of relapse post-ASCT were similar to our experience ranging from 33%-42%. As was described, during the past decade, salvage of relapsed FL-NT was constructive, as many patients had a response to a variety of therapies and some had more prolonged responses. We also found that a variety of therapies (ie, chemotherapy, radiation, antibody-directed therapy, an allogeneic stem cell transplant, or node removal) produced responses with some being durable. More recent therapies such as antibody-directed therapy and/or an allogeneic stem cell transplant were not significant in producing a remission >1 year nor were they predictive of long-term survival; however, these therapies have only become either acceptable or available late in the cohort. We may find that they have more of an impact over the next decade as their widespread use becomes more routine.

Finally, a similar percentage of patients died in both groups and have survived beyond 1 year. Therefore, despite the initial characteristics prior to relapse once the disease relapses after ASCT it may have similar characteristics regardless of the initial status prior to ASCT (FL-NT versus FL-T) and salvaging these patients is feasible as they do respond to conventional treatments, as has also been demonstrated by others, and a fraction can still have long-term survival [37,38]. However, despite improvements in the first-line treatments with combined modality therapies the lack of improvement over the past decade in treating those who have relapsed post ASCT is still a dilemma [51]. We would suggest that if patients have an acceptable performance status a trial of salvage therapy is worthwhile, regardless of the subtype at initial presentation.

The toxicity of the treatment under our conditions appeared to be relatively mild, both short-term and long-term. The immediate treatment-related toxicity, within the first 100 days of the treatment and NRM of 3% and 14%, respectively, is quite acceptable and in line with other centers [23,24,27,28,30,49,52,53]. Secondary malignancies/MDS post-treatment are always a concern and do make up the majority of the NRM (7% of 14%); however, this should be viewed in light of the work by Johnson et al. [13], where it was found that within a large cohort of patients with FL who received repeated courses of chemotherapy, without an ASCT, the rate of a secondary malignancy was 5%. Therefore, although the rate of secondary malignancies is higher, it is not much higher than what might be expected had they not had an ASCT confirming the acceptability of the toxicity of such an intensive treatment.

Therefore, our data suggest that an unpurged ASCT for relapsed, aggressive FL, transformed or not, is safe and continues to be an effective therapeutic tool in patients who have a reasonable performance status. It appears to change the natural history by increasing the median survival to 16 years, and is superior to conventional chemotherapy at any relapse. It also appears that some subgroups may have an excellent outcome such as those <40 years of age with chemosensitive disease. Finally salvage therapy for relapsed disease post-ASCT is also feasible.

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