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High-dose therapy and autologous stem cell transplant for transformed non-Hodgkin lymphoma in the rituximab era

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Abstract

The impact of rituximab on outcome of high dose therapy and autologous stem cell transplantation (HD-ASCT) for transformed NHL has not been previously described. We analyzed eighteen consecutive patients with indolent NHL who transformed to diffuse large B-cell lymphoma (DLBCL), received rituximab-containing therapy either before or after transformation and underwent subsequent HD-ASCT. With a median follow-up of 40 months, the 2-year PFS was 59% and the 2-year OS was 82%. Six patients did not receive rituximab pre-transformation; this group had a significantly better PFS at 2 years post HD-ASCT compared to 12 patients who were exposed to rituximab pre-transformation (p=0.03). HD-ASCT remains an effective therapeutic option for transformed NHL in the rituximab era. However, patients exposed to rituximab pre-transformation appear to have inferior HD-ASCT outcomes, and thus may benefit from novel conditioning and maintenance regimens in the setting of HD-ASCT.

Keywords

HD-ASCT; Transformed NHL; Rituximab; Transplant

INTRODUCTION

The natural history of advanced-stage, indolent non-Hodgkin's lymphoma (NHL) is characterized by a variable but usually long natural history, with improving survival over the past decade due in large part to the introduction of rituximab as part of standard therapy[1–2]. A major cause of morbidity and mortality in this group of patients is histologic transformation, or the evolution of indolent NHL to diffuse large B-cell NHL. Transformation occurs at a rate of approximately 3% per year, and arises from all subtypes of indolent B cell lymphoproliferative disorders[3–4]. Once transformation has occurred, the prognosis is generally poor, with a median survival after histologic conversion of approximately one year for patients with follicular lymphoma[5].

For younger patients with a favorable performance status, high-dose therapy with autologous stem cell transplantation (HD-ASCT) results in a prolonged progression-free survival (PFS) in a substantial subset, based upon retrospective single and multi-institutional experiences[6]. HD-ASCT may offer 5-year median progression free (PFS) and overall (OS)

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survival rates of up to 46% and 72%, respectively[6]. With the advent of Rituximab in the treatment of both *de novo* aggressive NHL and follicular lymphomas, PFS and OS have also improved. Rituximab improves PFS and OS in both follicular lymphoma and aggressive NHL when combined with chemotherapy[7–9], with complete responses (CRs) in approximately 75% of newly diagnosed patients with DLBCL. In patients with histologic transformation, R-CHOP has been shown to have a significantly higher rate of OS compared to patients receiving CHOP-like regimens without rituximab, as seen in a retrospective analysis evaluating the outcomes of 108 transformed patients (61% versus 33%)[10]. However, the impact of rituximab prior to transformation on outcome of HD-ASCT has not been previously reported. In this study, we describe the results of our single-institution 12-year experience in 18 patients receiving HD-ASCT for transformed lymphoma during the rituximab era, and compare the post HD-ASCT experience of those exposed to rituximab before transformation to those patients that were rituximab-naïve at transformation.

METHODS

Selection of Patients

Eligible patients were >17 years old with a documented transformed lymphoma (DLBCL) who were treated at the University of Rochester Medical Center (URMC) with ASCT between the years of 1998 – 2010. In this study, transformed lymphoma was defined as an initial biopsy proven diagnosis of indolent lymphoma with subsequent biopsy-proven diagnosis of DLBCL. The indolent NHL included low-grade follicular lymphoma (grade I, II, and NOS) and marginal zone lymphoma. Patients with discordant histology on presentation or whose transformation occurred within 6 months of the diagnosis of indolent lymphoma were excluded from the study. All patients had relapsed after standard chemotherapeutic regimens. For all patients, a minimal disease status had to be attained through chemotherapy, radiotherapy, or both prior to ASCT. Conditioning regimens at HD-ASCT were BEAM[11], BEAC and Cy/TBI.

All eligible patients were exposed to rituximab at some point prior to HD-ASCT. These patients were divided into two groups to compare those who were exposed to rituximab pre-transformation versus those who obtained rituximab only after transformation (Figure 1). The study was reviewed and approved by our institutional review board.

Evaluation and Statistical Methods

Progression free survival (PFS) was defined as time from HD-ASCT to date of disease relapse, progression, or death due to any cause. Patients still alive and without evidence of relapse at the end of follow-up were censored at their last documented URMC medical visit. Overall survival (OS) was calculated from the day of HD-ASCT until death or the date when the patient was last known to be alive. The median follow up time was also calculated from the day of transplantation. Kaplan-Meier survival curves were estimated, and differences in PFS between those who received rituximab prior to transformation versus those who were rituximab-naïve at transformation were assessed using the log-rank test. Additionally, we used standard Kaplan-Meier survival techniques and the log-rank statistics to evaluate univariate association of clinical characteristics at the time of HD-ASCT with PFS and OS. Statistical analysis was conducted using SAS statistical software (SAS, Cary, NC).

RESULTS

Patient Characteristics

18 patients (9 female) who had a history of indolent NHL in which the histology had transformed to DLBCL, underwent HD-ASCT between January 1998 and July 2010.

Baseline data for all 18 patients are presented in Table I. The median age at HD-ASCT was 58 years (range 40–65). Before histologic transformation, 5 patients had follicular grade I, 5 had follicular grade II, 6 had follicular lymphoma that was defined by pathology as low-grade (or either grade I or II), and 2 had marginal zone B-cell lymphoma. The median time from the diagnosis of indolent lymphoma to transformation was 4.2 years (range 0.7 – 23 years), and the median time from transformation to HD-ASCT was 6.5 months (range 3–88 months). At the time of his transplant, the single patient who experienced 88 months between transformation and transplantation was a 50 year old man who received 8 cycles of CHOP for transformed lymphoma. This patient remained in clinical remission for approximately 7 years, at which point he developed a recurrence, for which he underwent HD-ASCT.

Prior Therapy

All patients had previously received combination chemotherapy. Patients were treated with a median of 3 (range 1–9) chemotherapy regimens prior to HD-ASCT, including those prior to transformation. One or more common salvage regimens were used to achieve minimal disease response in this case series, including: ICE (Ifosfamide, Carboplatin, Etoposide) +/− Rituximab (9 patients), R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) (7 patients), and ESHAP (Etoposide, Methylprednisolone, Cytarabine, Cisplatin) (4 patients). 12 of the 18 patients had received rituximab containing regimens prior to transformation, while the other 6 never received rituximab prior to histologic transformation. There was no appreciable difference between these two study groups in terms of age, gender, number of previous chemotherapy regimens, use of anthracycline therapy, time from transformation to transplantation, and stage at diagnosis (Table I). However, the median time from indolent lymphoma diagnosis to transformation (6.4 years vs. 3 years) was longer among the rituximab-naïve group as compared to the patients that did receive rituximab-containing therapy prior to transformation. Conditioning regimens at HD-ASCT were BEAM (N=14), BEAC (N=1) and Cy/TBI (N=3). All except for one patient, who was Rituximab-naïve, achieved at least a partial or complete response prior to proceeding to obtain ASCT. This patient, who did not achieve a favorable response, experienced disease progression prior to obtaining ASCT.

Treatment Outcome

With a median follow-up time of 3.3 years (range: 2.8 months – 10.4 years), the 2-year PFS was 59% and the 2-year OS was 82% (Figure 2). Table II summarizes the outcomes of all 18 patients after HD-ASCT. There were no early treatment-related mortalities, and the majority of the patients remain alive without evidence of relapse (55.6%). Median follow-up time in the Rituximab naïve group and Rituximab-experienced group were 65 and 24 months respectively. Six patients (33.3%) relapsed after HD-ASCT (2 with indolent histologies and 4 with DLBCL); three of these patients have died. Two additional patients have died of myelodysplastic syndrome-acute myeloid leukemia after HD-ASCT. One such patient was a 57 year old woman at the time of her transformation, was Rituximab-naïve, received 3 different regimens of chemotherapy prior to her transplant, and was treated with a conditioning regimen with BEAM. The other patient who developed treatment-related MDS was a 64 year old man at the time of transformation, exposed to Rituximab by then, heavily pretreated with 5 different chemotherapy regimens prior to his ASCT, and was treated with a conditioning regimen consisting of TBI and Cytoxan.

Six patients did not receive rituximab for indolent disease prior to transformation; this group had a significantly better PFS compared to the12 patients who were treated with rituximab for indolent disease prior to transformation (p=0.03; Figure 3). There was no evidence of significant difference in 2 year PFS according to other clinical characteristics at the time of

HD-ASCT, including age, early vs. late transformation, number of prior chemotherapy regimens, time from transformation to HD-ASCT, disease stage at initial diagnosis, adjuvant radiation therapy, or conditioning regimen (Table III). However, power is limited to detect potentially relevant differences and the impact of these clinical factors on HD-ASCT outcomes in the transformed lymphoma population cannot be ruled out.

DISCUSSION

High dose therapy and autologous stem cell support (HD-ASCT) is a strongly suggested option by the NCCN guidelines for the treatment of patients with transformed lymphoma responding to salvage therapy[12]. The current literature on outcomes of HD-ASCT for transformed lymphoma is largely based upon data obtained prior to the rituximab era. Despite improved PFS and OS in both follicular and aggressive NHL with the introduction of rituximab to chemotherapy regimens, its impact prior to transformation on outcome of HD-ASCT has not been previously described. Our study is the first autologous transplant series of transformed lymphoma to limit inclusion to patients receiving rituximab pre-transplant, allowing us to evaluate the effect of rituximab therapy prior to transformation on HD-ASCT outcomes. Importantly, we limited this analysis to patients with biopsy-proven diagnosis of indolent lymphoma with subsequent biopsy-proven transformation to DLBCL. Some of the previously reported clinical transformed lymphoma series include patients for whom a biopsy was not mandated, but relied on a clinical picture consistent with histologic transformation, such as a sudden rise in LDH, rapid discordant localized nodal growth, new involvement of unusual extranodal sites, new “B” symptoms, or new hypercalcemia[4].

In our series of 18 histologically-confirmed transformed lymphomas treated with HD-ASCT, the 2-year PFS was 59% and the 2-year OS was 82%, with a median follow-up of over three years. The majority of our patients remain alive without evidence of disease. There were no early treatment-related mortalities. Consistent with the recent trend of improved PFS and OS in NHL with the introduction of rituximab to chemotherapy regimens, these results appear at least comparable or superior to those of the previously published case series of patients receiving autologous transplant for transformed lymphomas during the pre-rituximab era (outlined in Table IV)[13–18]. For example, in one retrospective study of 35 patients who received autologous bone marrow or blood stem cell transplants between the years of 1987 and 1989, the 2-year PFS and OS from transplant were estimated to be approximately 40% and 60% respectively; significant transplant related mortality, particularly among older patients, impacted the outcomes in this study[13]. In another study with 50 patients from the European Bone Marrow Transplant Registry with transformed lymphoma who underwent HD-ASCT prior to 1996 (pre-Rituximab era), the PFS and OS were approximately 40% and 60% respectively at 2 years[18]. In this registry series, transplant related mortality was higher than the current trial. Patients achieving complete remission prior to ASCT had the best outcome. St. Bartholomew’s Hospital[14] and Dana-Farber Cancer Institute[15] have reported similar outcomes of patients with transformed lymphoma treated with high dose cyclophosphamide conditioning with total body irradiation and autologous stem cell transplantation. In both of these studies, myelodysplasia was seen after transplantation, and the majority of the relapses were with transformed lymphoma. Of note, the risk of myelodysplastic syndrome and acute leukemia as a consequence of autologous transplantation appears to be highest in heavily pretreated patients when total body irradiation is included in conditioning regimens[19–20]. In our current study, similar to the published experiences, two patients have developed myelodysplasia, one of whom had conditioning including total body irradiation. Finally, in the rituximab era, patients treated at Cleveland Clinic for transformed lymphoma had superior outcomes than a cohort of patients with relapsed diffuse large B-cell lymphoma[21].

Overall, our results compare favorably to these historical experiences, which is consistent with the recent trend of improved PFS and OS in NHL with the introduction of rituximab to chemotherapy regimens. However more importantly, we observed that patients who were rituximab-naïve prior to transformation had significantly improved PFS relative to those who were exposed to rituximab-containing therapy prior to transformation. This finding suggests that despite overall improved outcomes for patients administered rituximab for the treatment of transformed disease, the subset of patients exposed to rituximab prior to transformation may have inferior outcomes compared to the patients who are naive to rituximab-containing chemotherapy regimens prior to transformation. This observation is similar to the recently published experience of patients with *de novo* diffuse large B-cell NHL treated with rituximab prior to HD-ASCT in the CORAL study[22], where PFS following HD-ASCT was inferior in patients exposed to rituximab prior to relapse of DLBCL. Interestingly, Tan and colleagues[23] also have demonstrated a superior overall survival, in a cohort of patients with transformed lymphoma treated with ASCT, for patients who were chemotherapy naïve at the time of transformation compared with those patients who were previously treated. Our study may be vulnerable to a selection bias, since patients who were not previously exposed to rituximab were diagnosed earlier than the patients who had received rituximab prior to transformation. Since the risk of transformation over time appears continuous, at least through 15 years[35], it is possible we may be selecting earlier, and potentially more aggressive transformation, in the recent cohort. Whether this has implications on the outcome after HD-ASCT is not known, and will require further follow-up and validation in larger cohorts of patients.

It is unknown whether the mechanisms of resistance to rituximab are different from resistance to chemotherapy agents[24]. In our study, the majority of the patients had significant exposure to both chemotherapy and rituximab prior to transformation. These patients appear to represent a particularly high risk group, where even with HD-ASCT, the relapse rate remains high. Indeed, the rituximab naïve patients in our series had the longest follow-up, and still had superior prognosis compared with patients who had extensive prior therapies containing rituximab. Moreover, studies from the pre-rituximab era indicate that 30% of patients with transformation are not eligible for HD-ASCT, emphasizing the challenge of treating these patients[25]. Future studies should evaluate whether these refractory patients have unique cytogenetic and molecular profiles suggesting novel targets for therapeutic intervention. These patients may benefit from novel conditioning and maintenance regimens in the setting of HD-ASCT. One possible option for these patients is to include radioimmunotherapy in the conditioning regimens at ASCT. Both ibritumomab tiuxetan and iodine-131 tositumomab have activity for the treatment of transformed lymphoma[26]. Several groups have evaluated non-myeloablative and myeloablative radioimmunotherapy as part of ASCT for follicular and transformed lymphoma, with promising early results[27–28]. Our findings would suggest that patients with transformed lymphoma exposed to rituximab prior to transformation may be particularly suited for this novel approach. Alternatively, these patients may be considered for non-myeloablative allogeneic transplantation, which in several series has resulted in favorable disease control in small numbers of patients with transformed disease[29–31]. In a recent allogeneic series of transformed NHLs from Vancouver, 30% of patients received rituximab prior to transplant; the overall survival was 39% at two years. Similar to the other allogeneic series, transplant related mortality was 36% at 3 years[32]. In a recent preliminary analysis by the Canadian Blood and Marrow Transplant Group, outcomes were similar following allogeneic and autologous stem cell transplantation, with 5-year post-transplant OS 46% vs 50% and PFS 46% vs 48%, respectively[33]. All of these allogeneic series consist of highly selected younger patients, and whether the preliminary favorable results are generalizable will require prospective multi-center trials.

In conclusion, we demonstrate the continued utility of ASCT as therapy for transformed lymphoma in the rituximab era. This well tolerated treatment provides longstanding disease control, with minimal transplant-related mortality. As observed in other series, patients previously exposed or refractory to rituximab represent a particularly challenging group, and should be the focus of continued clinical trial efforts.

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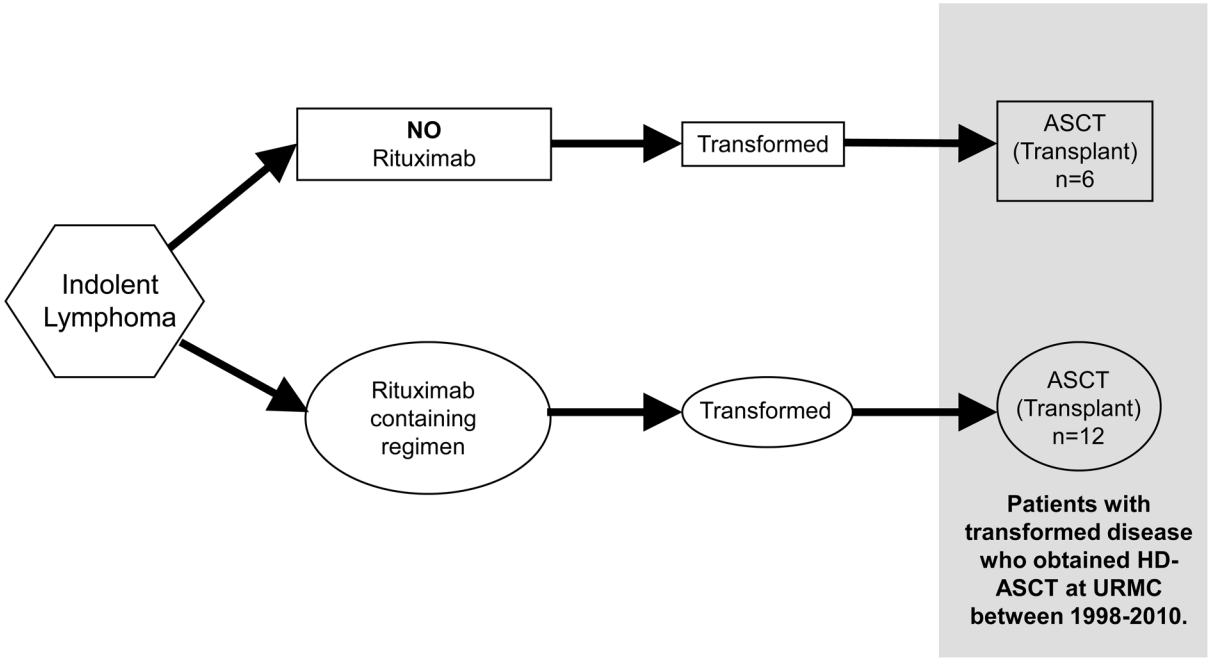

Figure 1.

Treatment course, response and outcomes. Patients with transformed disease who obtained HD-ASCT at URMC between 1998–2010 were selected for this retrospective analysis. These patients were divided based on their treatment history prior to transformation (ritixumab naïve vs. rituximab-exposed). Median follow-up time was 40 months.

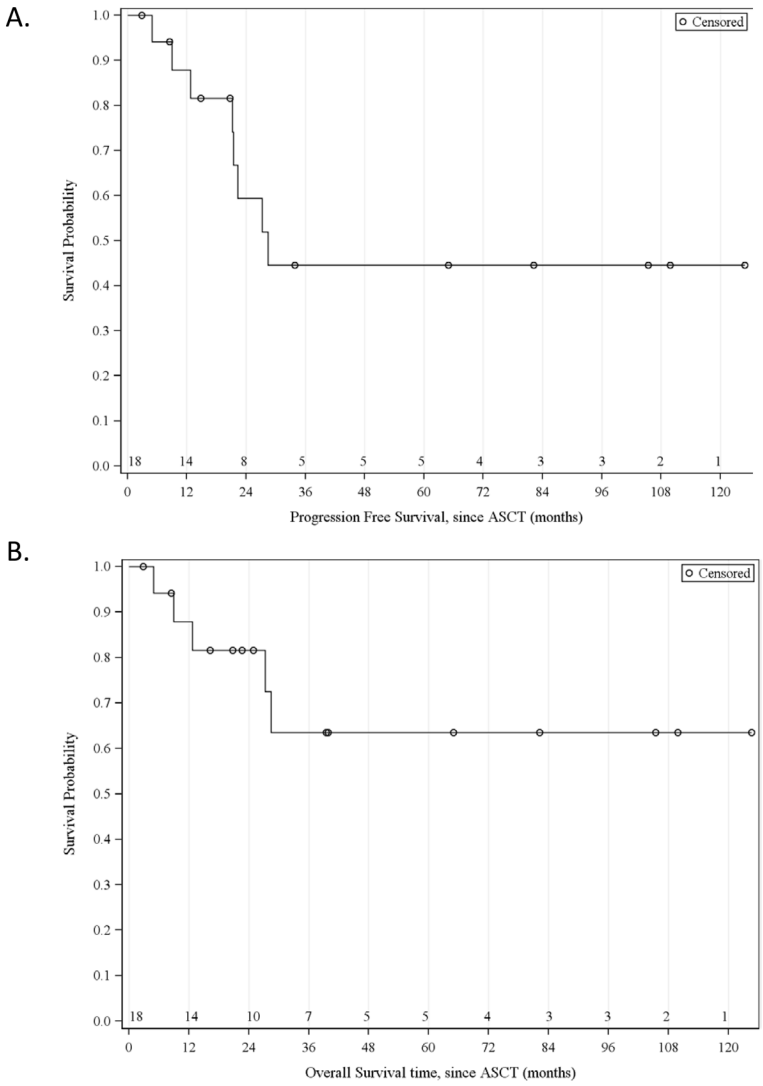

Figure 2.

Kaplan-Meier estimates of A) Progression Free survival, PFS (months; N=18); and B) Overall Survival, OS (months; N=18)

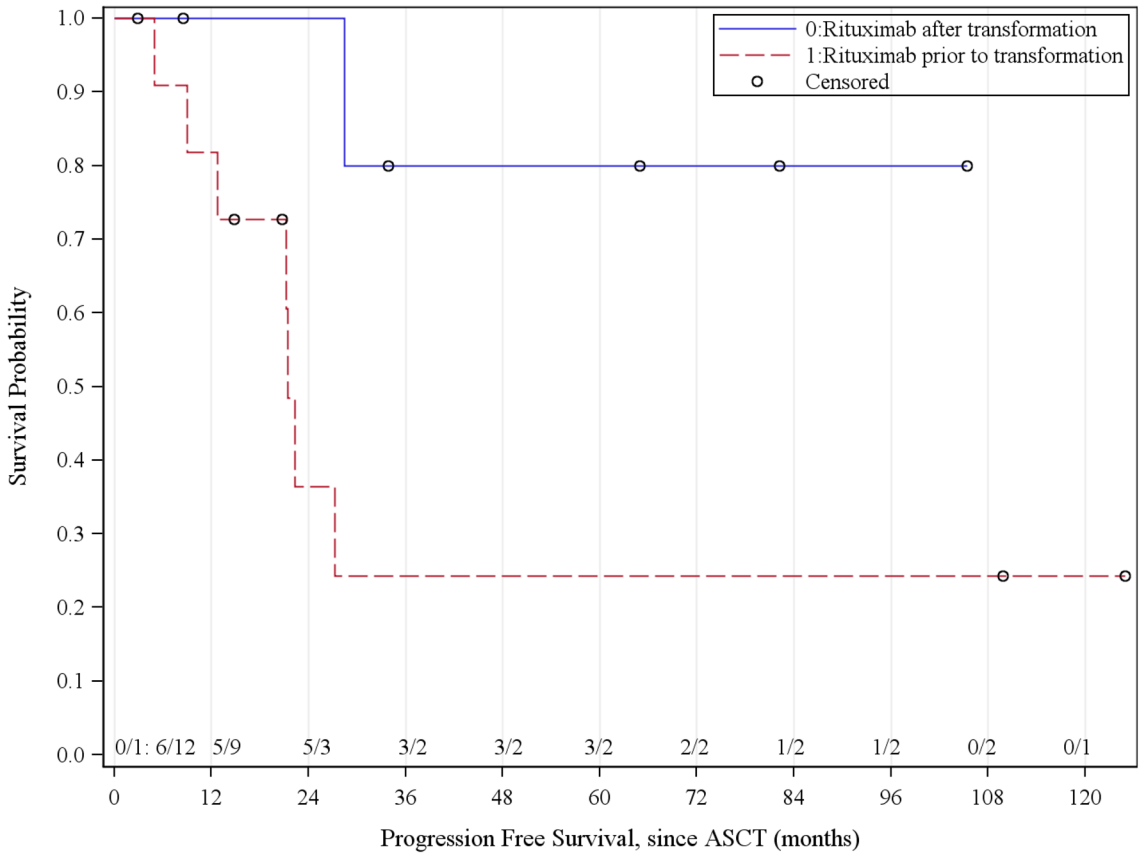

Figure 3.
Kaplan-Meier estimates Progression Free Survival among patients exposed to rituximab prior to transformation (N=12) as compared to those who were exposed to rituximab after transformation (N=6)

Table I

Patient Characteristics

Characteristic	All Patients (n=18)	Range	Rituximab naïve at Transformation (n=6)	Range	Prior Rituximab at Transformation (n=12)	Range
Age at Transplant (median)	**58**	40 – 65	**59**	48 – 61	**56**	40 – 65
Female (%)	**9 (50%)**		**3 (50%)**		**6 (50%)**	
Number of Previous Chemotherapy						
Regimens (median, range)	**3**	1 – 9	**2.5**	1 – 5	**3**	1 – 9
Prior to Transformation	**1**	0–8	**0.5**	0 – 1	**1**	0–8
Between Transformation & Transplant	**1**	1–4	**2**	1 – 4	**1**	1 – 2
Prior use of Anthracyclines	**15 (83%)**		**5 (83%)**		**10 (83%)**	
Time from Indolent Lymphoma to Transformation (median, range; years)	**4.2**	0.7 – 23	**6.4**	2 – 23	**3**	0.7 – 20
Time from Transformation to Transplant (median, range; months)	**6.5**	3 – 88	**9**	3.5 – 88	**6.25**	3 – 12
Partial or complete response prior to ASCT	**17 (94%)**		**5 (83%)**		**12 (100%)**	
Median follow-up time (months)	**40**	2.8 – 124.6	**65**	8.5 – 105.4	**24**	2.8 – 124.6
Histology prior to Transformation (%)						
Follicular Grade I	**5**		**1 (6%)**		**4 (22%)**	
Follicular Grade II	**5**		**1 (6%)**		**4 (22%)**	
Low Grade Follicular NOS	**6**		**4 (22%)**		**2 (11%)**	
Marginal Zone B-cell Lymphoma	**2**		**0 (0%)**		**2 (11%)**	
Stage at Diagnosis of Indolent Lymphoma (%)						
I,II, III	**5**		**4 (67%)**		**1 (8%)**	
IV	**9**		**2 (33%)**		**7 (58%)**	
Unknown	**4**		**0 (0%)**		**4 (33%)**	

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Table II

Summary of Outcomes post HD-ASCT (N=18; median follow-up = 3.3 years)

Characteristic	N=18	%
Alive without evidence of relapse	10	55.6%
Relapses Post ASCT	6	33.3%
Indolent histology at relapse	2	
Times of relapse after ASCT	12 & 3 months	
Aggressive histology at relapse	4	
Times of relapse after ASCT	3, 7, 22, & 22 months	
Deaths following relapse	3	16.7%
Progressive NHL (aggressive histology)	2	
Progressive NHL (indolent histology)	1	
Deaths among patients without evidence of relapse post ASCT	2*	11.1%

*Both deaths due to myelodysplastic syndrome

Table III

Univariate Analysis of Baseline Predictors of PFS following HD-ASCT for transformed NHL

Baseline Factor	Level	N	Events	2 year PFS	*p*-value*
Rituximab Prior to transformation	Yes	12	7	36.4%	**0.0341**
	No	6	1	100%	
Age at Transplant	>55	10	5	65.6%	0.7159
	≤55	8	3	51.4%	
Late Transformation (> 3 yrs from initial diagnosis)	Yes	11	5	64.9%	0.9938
	No	7	3	50.0%	
Number of Prior Chemotherapy Regimens	>3	6	3	62.5%	0.7397
	≤3	12	5	58.4%	
Time from Transformation to Transplant	>6.5 months	8	2	66.7%	0.1681
	≤6.5 months	10	6	54.0%	
Stage at Initial Diagnosis	IV	9	4	50.0%	0.3824
	I/II/III	5	1	100%	
Radiation	Yes	7	5	34.3%	0.0666
	No	9	2	85.7%	
BEAM	Yes	14	7	43.2%	0.1507
	No	4	1	100.0%	

*P-value corresponding to log-rank statistic; some factor levels do not add up to 18 due to missing data

Table IV

Autologous transplant series for transformed lymphomas during the pre-Rituximab era (adapted from Bernstein *et al*[6])

Study	n	Median follow-up (yrs)	OS	PFS/EFS/DFS
Chen [13]	35	4.3	2 yr: ~60% * 5 yr: 37%	2 yr PFS: ~40% 5 yr PFS: 36%
Foran[14]	27	2.4	Median: 8.5 yr	N/A
Friedberg[15]	27	3.0	5 yr: 58%	5 yr DFS: 46%
Ramadan[16]	33	1.7	2 yr: 72% 5 yr: 72%	2 yr EFS: 47% 5 yr EFS: 33%
Sabloff [17]	23	7.6	2 yr: ~70% * 5 yr: 56%	2 yr PFS: ~40% 5 yr PFS: 25%
Williams[18]	50	4.9	2 yr: 64% 5 yr: 51%	2 yr PFS: ~40% 5 yr PFS: 30%

OS indicates overall survival; PFS, progression-free survival; EFS, event-free survival; DFS, disease-free survival; N/A: data not available.

* This number was extrapolated from the survival curves.