

# Autologous Stem Cell Transplantation for Transformed Lymphoma: Single-Center Experience

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**ABSTRACT:** This is a single-center review of retrospectively collected computerized data and medical records of all the patients who have undergone high dose chemotherapy and ASCT for transformed lymphoma from 1999–2014. The primary endpoint of the study was overall survival (OS) and secondary endpoint was progression free survival (PFS). A total of 27 patients with histological transformation were identified. This included transformation from follicular lymphoma Grade 1–3A and non-follicular indolent lymphoma, synchronous and asynchronous presentation. All transformed to diffuse large B cell lymphoma. 33% were chemotherapy naive prior to transformation. Median follow up was 47 months. For the entire cohort OS at 3 years was 73% and PFS = 82%. The treatment has low risk for nonrelapse mortality providing durable remission.

**KEYWORDS:** transformed lymphoma, autologous stem cell transplantation

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## Introduction

Indolent lymphomas have a risk of transformation into an aggressive histology. The most common subtype of indolent lymphoma, follicular lymphoma (FL), has an incidence of transformation of ~3% per year.<sup>1</sup> The evolution of indolent lymphomas transforming to an aggressive lymphoma is the major cause of morbidity and mortality. In the past decade, the median overall survival (OS) has improved from one year to approximately five years.<sup>2</sup> New modalities of therapy and earlier diagnosis of histological transformation (HT) could be the attributing factors. Due to the aggressive nature of transformed lymphomas (TLs), many centers offer high-dose chemotherapy and autologous stem cell transplantation (HD-ASCT) to eligible patients with chemotherapy-sensitive disease. The benefits of autologous over allogeneic transplantations included superior OS and significantly less treatment-related mortality.<sup>3,4</sup> The use of rituximab in pretransplant therapy is considered to be responsible for improved outcomes.<sup>5</sup> The National LymphoCare Study confirmed that the incidence of transformation in the current era remains the same despite the use of chemoimmunotherapy.<sup>2</sup>

The gold standard for the diagnosis of HT is documentation by biopsy. The yield is enhanced by positron emission tomography scan (PET) assessment. Clinical characteristics that correlate with transformation are hemoglobin <12 g/L, elevated lactate dehydrogenase, age >60 years, and high International Prognostic Index score.<sup>6</sup> The presence of indolent lymphoma at diagnosis of transformation (synchronous) is associated with

poor performance status in 33%, disseminated disease in 97%, more than one extranodal site in 50%, and increased lactate dehydrogenase level in 55%.<sup>7</sup> At the Saskatoon Cancer Centre, patients with TL who underwent HD-ASCT after showing chemotherapy sensitivity were analyzed retrospectively.

## Methods

The study population consisted of transplant eligible patients diagnosed with TL. The data were retrospectively collected from the computerized database and medical records. The study was approved by the Biomedical Research Ethics Board of the University of Saskatchewan.

A total of 27 patients had histological proof of transformation, including 4 patients with synchronous transformation. All the transformations were diffuse large B-cell lymphoma (DLBCL). Patients received treatment with rituximab-based chemotherapy and ASCT for TL between 1999 and 2014.

Patients excluded from the study were those with FL grade 3B, CLL/SLL, those who received autologous followed by allogeneic transplantation, or those who had undergone transplantation prior to transformation.

On diagnosis, each patient had staging investigations that included computed tomography (CT) scan (one had PET scan), bone marrow aspiration and biopsy, and relevant blood work. Details of previous treatments for indolent lymphoma, age at diagnosis of the indolent lymphoma and the transformation, and time from diagnosis of transformation till ASCT were noted.



All patients received rituximab-based chemotherapy, primarily the R-CHOP protocol, but others received R-DHAP, R-GDP, R-ICE, or R-ESHAP. Response to chemotherapy was classified as complete response (CR), partial response (PR), stable disease, or progressive disease (PD) according to the criteria proposed by the International Working Group criteria.<sup>8</sup> If PR was not achieved following rituximab-based chemotherapy, they received salvage treatment to demonstrate chemosensitivity before proceeding to ASCT. Only patients who attained PR were eligible for ASCT.

Patients responding to chemotherapy underwent peripheral stem-cell mobilization with cyclophosphamide 2 g/m<sup>2</sup> i.v. day 1, etoposide 200 mg/m<sup>2</sup> i.v. days 1–3, and filgrastim 10 µg/kg/day s.c. starting on day 6 and continued until the day of completion of apheresis or harvest. If peripheral blood stem-cell collection was inadequate (<2.0 × 10<sup>6</sup> CD34<sup>+</sup> cells/kg), peripheral stem-cell mobilization with plerixafor (0.24 mg/kg) was undertaken.

The preparative regime used prior to ASCT was carmustine (300 mg/m<sup>2</sup>) one day, etoposide (200 mg/m<sup>2</sup>) and cytosine arabinoside (200 mg/m<sup>2</sup>) over four days, and melphalan (140 mg/m<sup>2</sup>) over one day (BEAM).<sup>9</sup> Response to treatment was assessed at three months posttransplantation by CT scan (six had PET scans to confirm findings).

The primary end point of the study was OS, calculated from the date of ASCT to the date of last follow-up or death resulting from any cause (PD, treatment, or transplantation related or unrelated cause). As a secondary end point, progression-free survival (PFS) was calculated from the date of ASCT to the date of first subsequent relapse or death resulting from any cause. Patient characteristics at diagnosis, transformation, and transplantation were documented. All survival probability curves were estimated using the Kaplan–Meier method. *P* value <0.05 was considered statistically significant. The statistical software SAS V9.3 was used for the analysis.

## Results

A total of 27 patients with HT were eligible for analysis. Their clinical characteristics are outlined in Table 1.

The majority transformed from FL (22/27), while five patients transformed from non-FLs. Four patients had synchronous transformation, while the rest had asynchronous transformation. Three transformations were synchronous with FL, while one was with MZL. All the patients transformed to DLBCL.

The mean age at transformation was 53 years (range 40–69 years). The majority of patients (18/27) had received at least one line of chemotherapy prior to transformation, which was rituximab-based chemotherapy in 12 patients. A total of nine (33%) patients were chemotherapy naive prior to transformation (including four with synchronous transformation). In six patients, treatment included radiation therapy.

The mean time to transformation was 58 months. Patients received ASCT in the mean time of 6.5 months from the diagnosis of transformation. Prior to ASCT, all had

**Table 1.** Patient characteristics and outcomes.

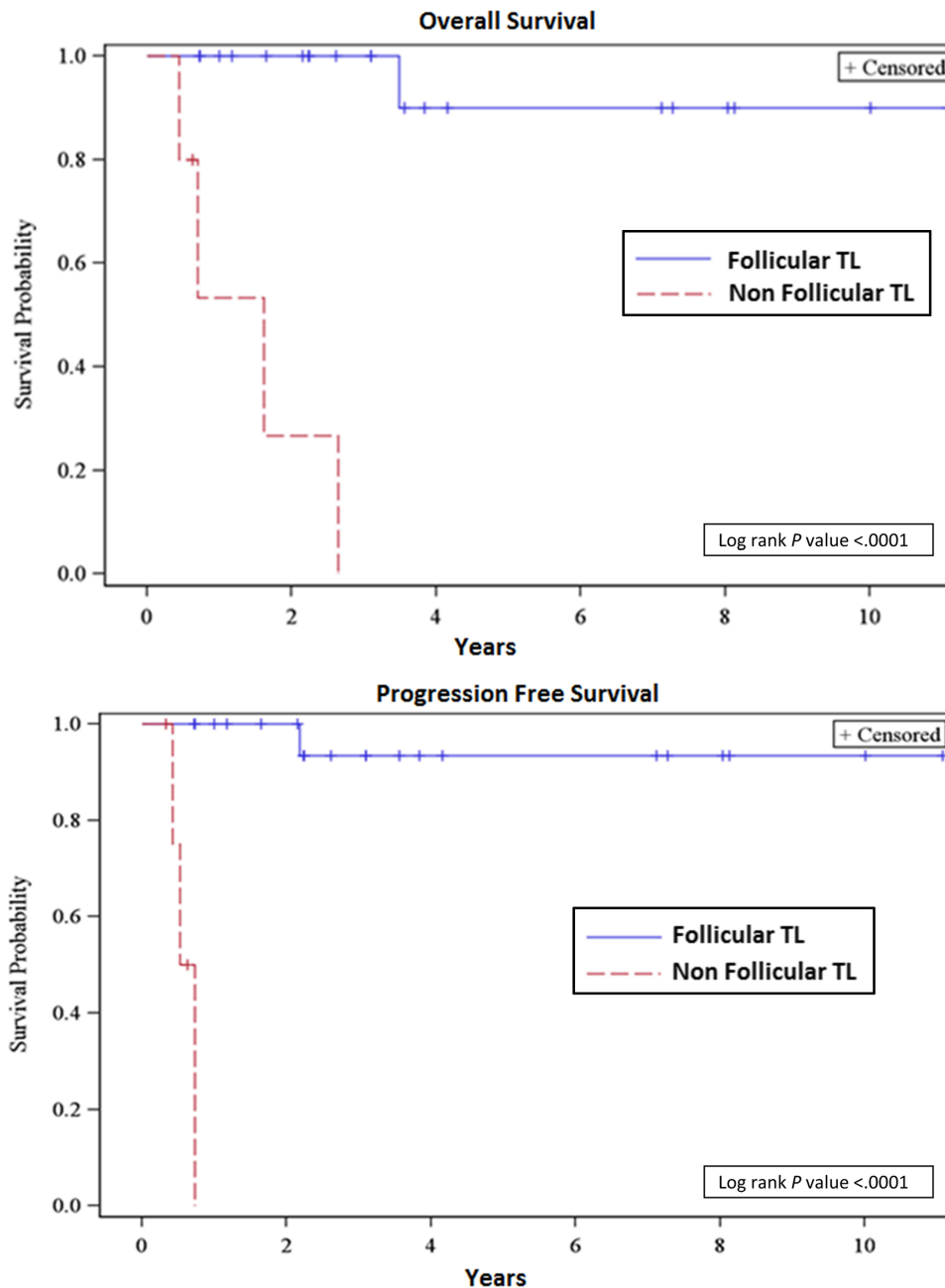
Total number of patients		27
Gender	M/F	16/11
Year of diagnosis of indolent lymphoma	• 1990–1999	4
	• 2000–2004	12
	• 2005–2014	11
Age at diagnosis of indolent lymphoma (years)	Mean (range)	53 (40–66)
Age at diagnosis of transformed lymphoma (years)	Mean (range)	58 (42–67)
Histology indolent lymphoma	Follicular/ non-follicular	22/5
Histology TL	Asynchronous/ synchronous	23/4
Prior chemotherapy treatment	Rituximab based	12
	1	11
	2	6
	>3	1
	None	9
Prior radiation therapy		6
Time to transformation (months)	Mean/range	58 (0–153)
Time to ASCT (months)	Mean/range	6.5 (4–8)
HD-ASCT outcome	CR	20
	SD	2
	PD	5
Died		6
Treatment related mortality		0
Median follow up from date of ASCT (months)		47

**Abbreviations:** TL, transformed lymphoma; CR, complete remission; SD, stable disease; PD, progressive disease.

rituximab-based chemotherapy. R-CHOP regime was used in 12 patients, R-DHAP regime was used in 4 patients, and R-ICE and R-GDP regimes were used in 5 patients each. One patient had R-ESHAP. The various chemotherapy regimens did not impact the outcome.

For the entire cohort, posttransformation OS at three years is 73% with the PFS of 82%. The posttransformation OS and PFS showed a significant difference when the patients were stratified by transformed FL or nonfollicular. The three years OS and PFS for transformed FL is 90% and 93%, respectively (Fig. 1).

In sharp contrast to the patients with transformed FL, we had five patients in this cohort diagnosed with non-FL. Two patients had marginal zone lymphoma, one patient had lymphoplasmacytic lymphoma, one patient had MALT, and one patient transformed from Hodgkin lymphoma. Only one patient with synchronous marginal zone lymphoma and DLBCL has maintained CR 18 months post-ASCT. The difference between the two groups is significant with log-rank *P* value = < 0.0001. The comparison is unbalanced due to the small sample size in the transformed non-FL.



**Figure 1.** Overall survival and progression-free survival of follicular vs nonfollicular transformed lymphoma.

We found no significant difference in the outcomes of patients who received chemotherapy or were chemotherapy naive (Fig. 2). Patients who did not receive rituximab prior to transformation appeared to have an OS advantage. However, this is not significant as the log-rank  $P$  value was 0.06 (Fig. 3). The total number without prior rituximab administration for indolent lymphoma is 12. This includes nine patients who were chemotherapy naive and four patients with synchronous presentation.

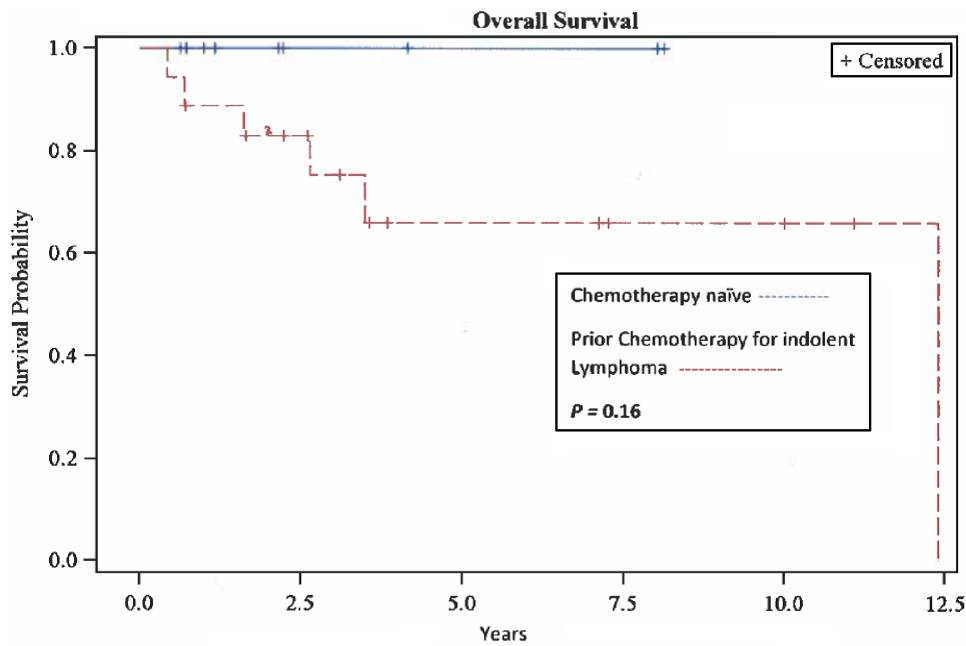
A total of six patients died, of which five patients died from PD more than three months posttransplantation. One patient died 12 years posttransplantation in CR. He had recurrence of colon cancer. Four out of five patients who died

with PD had transformation from non-FL. There were no treatment-related mortalities.

## Discussion

HT of indolent B-cell lymphoid malignancies impacts the natural course of the disease dramatically. The pathogenesis is not yet clearly defined but data from the rituximab era show an improvement in survival.

Historical studies of TL reported five-year OS between 40% and 70%.<sup>1,3,6,10</sup> The CIBMTR analysis showed ASCT in comparison to allogeneic stem cell transplantation for transformed FL provides durable remissions with considerably reduced treatment-related mortality.<sup>3</sup> A recent study of

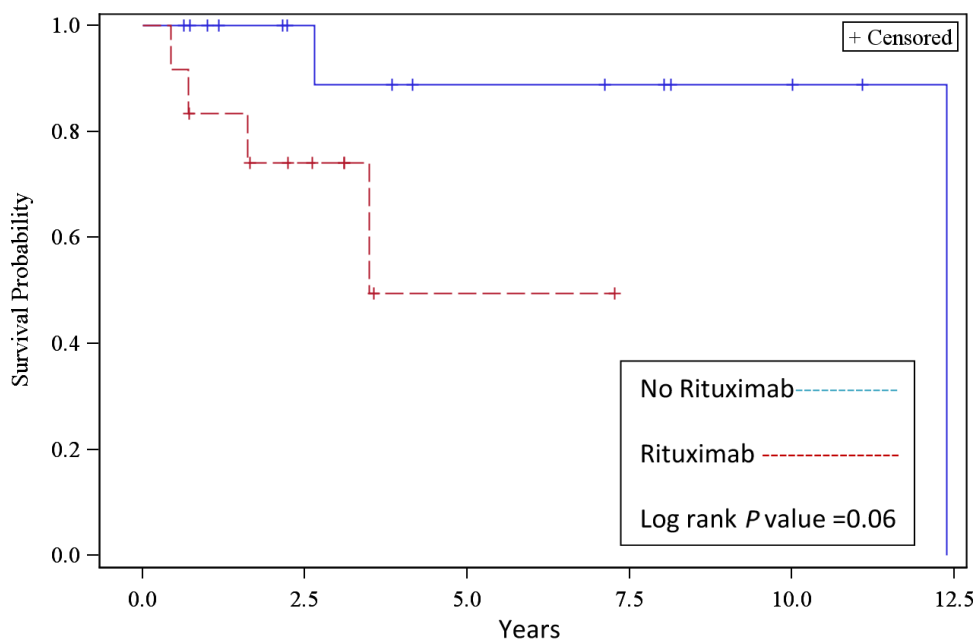


**Figure 2.** Overall survival stratified by chemotherapy.

transformed FL from the National LymphoCare Study database analyzed 379 patients (only 6 patients underwent ASCT). The OS at five years was 50%, and the data demonstrate that patients with synchronous transformation of FL had outcomes comparable to FL without transformation (five-year OS of 88%).<sup>2</sup> The NCCN study observed that younger chemotherapy-naïve or rituximab-naïve patients had a favorable outcome without transplantation with the five-year OS of 80%.<sup>11</sup> University of Iowa/Mayo Clinic observed that those who transformed early in the disease (<18 months) had a poor prognosis.<sup>12</sup>

A detailed study by Maeshima et al<sup>13</sup> on transformed FL histopathological parameters influencing survival showed that asynchronous histology has a worse prognosis than those with synchronous presentation. Those with three or more regimens of chemotherapy had a shorter OS attributed to chemoresistance. As subtypes of TL are defined with superior diagnostic technology, the precise timing and role of ASCT for TL in the rituximab era are yet to be determined.

Most of the studies on TL are retrospective with considerable extrapolation from studies on DLBCL. The Norwegians



**Figure 3.** Overall survival stratified by prior rituximab administration.

undertook the first prospective phase II study of HD-ASCT for TL which showed a two- and five-year OS = 73% (95% CI 0.57–0.89) and 47% (95% CI 0.29–0.65).<sup>14</sup> PFS at two and five years is 50% (95% CI 0.32–0.68) and 32% (95% CI 0.18–0.46). However, in this study, only five patients had received rituximab prior to transformation.

Our observational retrospective single-center study contributes to the data on TLs in the rituximab era. The OS and PFS showed a significant difference when comparing FL vs nonfollicular TL. The nonfollicular TL group is a small sample size with insufficient statistical power for accurate evaluation and should be validated with further studies.

A Canadian and Australian collaboration published a multicenter study of nonfollicular TL undergoing ASCT and reported no significant variation in the OS of nonfollicular and follicular TLs.<sup>15</sup> They had a total of 22 patients with nonfollicular TL undergoing ASCT with OS and PFS, which was similar to follicular TL; however, unlike our series, transformed patients from CLL/SLL were included in this study.

Designating the indolent non-FLs in one group is not a true representation for accurate analysis. Each of the different types of indolent non-FLs is of a different pathogenesis, varies in natural history, and is treated with specific chemotherapy regimens. Combining them into one group for analysis could obliterate the discerning factors. A larger sample size of the different subtypes with randomized study design, though difficult to obtain, will be necessary to assess the benefit of ASCT in transformed non-FLs.

Our improved outcomes of OS and PFS in follicular TL are a highly selected group of younger and otherwise healthy patients, eligible for ASCT with chemosensitive disease. The treatment options and physician choices were uniform for the cohort in a single center.

## Conclusion

The benefit of HD-ASCT for patients with transformed FL is demonstrated. This treatment has low risk for nonrelapse mortality and provides durable remission. The poor outcome seen in patients with nonfollicular TL needs further validation.

The newer treatment regimens, such as bendamustine/rituximab, as well as protocols for conditioning (bendamustine—BEAM), may demonstrate improved outcomes. Novel agents currently investigated in maintenance therapy post-ASCT with immune modulators (lenalidomide), PD-1 inhibitors, Bruton tyrosine kinase inhibitors, Aurora A kinase inhibitors, and mTOR/PI3K inhibitors for DLBCL and indolent NHL are potential treatment options, which could alter the role of ASCT.<sup>16–19</sup> The need for prospective randomized controlled trials on TL is apparent.

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## Author Contributions

Designed the study: VS, ME, and WS. Conducted the data analysis and prepared the article: VS. Performed the statistical analysis: SS and RA. Edited the article: JS and MB. All authors reviewed the final article and approved the submitted version.

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