Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2012 December ; 12(6): 406–411. doi:10.1016/j.clml.2012.07.003.

Superior long term outcome of patients with early transformation of non-Hodgkin lymphoma undergoing stem cell transplantation

Nishitha Reddy, Olalekan Oluwole, John P Greer, Stacey Goodman, Brian Engelhardt, Madan H. Jagasia, and Bipin N Savani

Hematology and Stem Cell Transplantation Section, Division of Hematology/ Oncology, Department of Medicine, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA

Abstract

Transformed non-Hodgkin's lymphoma arising from follicular lymphoma (TL) carries a poor prognosis with a median survival time after transformation reported to be around a year. Fifty one consecutive patients with TL received stem cell transplantation (SCT) between January 2000 and December 2010 (autologous [auto-SCT] 44, allogeneic SCT [allo-SCT] 7). Thirty six (70.5%) patients had an early transformation, defined as histological evidence of transformation at the time of initial diagnosis or transformation within one year of follicular lymphoma. Fifteen patients had early stage disease (29%) and 36 (71%) with advanced stage disease on presentation. At the time of analysis, 37 patients were alive with an estimated 5 year overall survival (OS) and event free survival (EFS) of 61.8% and 45% respectively. OS and EFS were not significantly different between types of transplant procedure. The major cause of transplant failure was disease recurrence, with estimated 2 year relapse rate of 37.4%. Importantly, early transformation was independently associated with improved OS (HR 3.29, $p=0.028$) and EFS (HR 2.49, $p=0.029$). Our results indicate that aggressive transplant approach should be considered upfront in patients with TL and emphasize the need to incorporate novel strategies (e.g. immunomodulation) early post-SCT to prevent relapses as disease recurrence remains the major cause of failure in heavily pre-treated patients.

Keywords

autologous stem cell transplant; allogeneic stem cell transplant; radioimmunotherapy; transformed Lymphoma

Correspondence: Nishitha Reddy, MD, MSCI, Division of Hematology and Oncology, Department of Medicine, Vanderbilt University Medical center, 1301 Medical Center Drive; 3927 TVC, Nashville, TN-37232, Nishitha.Reddy@Vanderbilt.Edu, Phone #: 615-936-0381, Fax #: 615-936-1812.

Declaration of commercial interest: None

Introduction

With the changing natural history of follicular lymphoma, in the era of monoclonal antibody therapy, the true incidence of histological transformation is unclear. Previous studies report that the histological transformation of an indolent follicular lymphoma to a high grade lymphoma (TL) occurs at a rate of 3% per year. The prognosis for TL is generally poor with rapid progression of the disease. Most of these studies performed in the pre-rituximab era report 5 year survival rates of 55–65% for early stage and 15–25% for late stage disease.^{1–5}

Standard chemotherapy and radioimmunotherapy have offered promising responses however; the duration of response does not appear to last long.^{6–9} Several studies evaluating the role of autologous stem cell transplantation (auto-SCT) as a salvage regimen have indicated that a subset of patients benefit from this modality of treatment.^{4;10–13} With an improvement in supportive care, outcome after allogeneic stem cell transplantation (allo-SCT) has improved significantly over the past decade.^{14;15} Successful results have been reported in selected patient populations who have achieved long-term disease free survival (DFS) after allo-SCT.⁴

The major limitation of prior studies include short follow up and lack of long term outcome data on patients receiving SCT with regards to timing of transformation (early vs. late TL). In the era of emerging novel therapies, the actual timing, optimal conditioning regimens and long term impact of the type of stem cell transplantation is unclear.^{3;4}

Here we report one of the largest series exclusively of patients undergoing SCT for TL in the rituximab era. We hypothesize that patients who present with early transformation have a better prognosis with an aggressive treatment modality.

Patients and methods

Fifty one consecutive patients older than age 18 years with a confirmed diagnosis of TL receiving high dose chemotherapy and SCT between January 2000 and December 2010 at Vanderbilt University Medical Center adult transplant program, were included in this study (Table 1). All patients received planned rituximab based chemotherapy pre-SCT. Patients were required to have chemotherapy-sensitive disease documented pre-SCT after salvage chemotherapy. This study was approved by the Institutional Review Board of Vanderbilt University Medical Center. All patients provided informed consent in accordance with the Declaration of Helsinki.

Clinical information was reviewed, and baseline characteristics including common pre-transplant and transplant variable information was recorded. Disease progression, overall survival (OS), event free survival (EFS), non-relapse mortality (NRM) and relapse rate were defined by standard criteria. Event free survival was defined as the time from transplantation to the occurrence of disease relapse or secondary malignancy.

Histological transformation

Published criteria were used to define histological transformation.^{1;4;16} A diagnosis of follicular low grade (1–2) lymphoma followed by a transformation to an intermediate

(diffuse large B-cell, DLBCL) or an aggressive (Burkitt) lymphoma was referred to as transformed lymphoma (TL). Progression from FL grade 1 or 2 to FL grade 3 was not considered as transformation; however, progression from FL grade 3 to a frank DLBCL was considered TL.

Stem cells were collected using approved institutional peripheral blood stem cell mobilization protocols. All patients received standard care per institutional protocol regarding antimicrobial prophylaxis, surveillance cultures, monitoring for viral infections, and treatment.

Early vs. late Transformation

Early transformation was defined as patient in whom there was histological evidence of transformation at the time of diagnosis or transformation within one year. Patients who have had transformation more than a year after initial presentation were defined as late transformation.

Transplantation procedures

Auto-SCT—Stem cells were mobilized using high dose chemotherapy (cyclophosphamide) and G-CSF or G-CSF alone. CBV (cyclophosphamide 7200mg/m², etoposide 2000 mg/m², and BCNU 400 mg/m²) was most commonly used (88%) conditioning regimen in patients receiving auto-SCT.

Allo-SCT—Four patients received reduced intensity conditioning (RIC) and 3 myeloablative regimen followed by either matched related (n=3) or unrelated donor (n=4) peripheral blood stem cell transplantation (PBSCT). All patients received GVHD prophylaxis with calcineurin inhibitor and either methotrexate (myeloablative conditioning) or mycophenolate mofetil (RIC). The diagnosis and grading of acute and chronic GVHD were based on standard criteria.

Response criteria

Response criteria were based on guidelines from the International workshop on non-Hodgkin lymphoma (NHL). Complete remission (CR) was defined as complete radiological regression of all previous measurable disease or bone marrow involvement. Partial response (PR) was defined as a reduction of 50% or greater reduction in the sum of the products of the longest and perpendicular diameter of measurable lesions within a 30-day period prior to transplant and at days +30 and +100. Based on these criteria, all data were individually verified regarding the best response status prior to SCT.

Statistical Analysis

Patient characteristics were compared between the two SCT groups by t-test as appropriate. OS, EFS, NRM and relapse was reported using Kaplan–Meier analysis. The difference between survival curves was tested for statistical significance using log rank test. Univariate analysis was performed with disease and transplantation related variables to see the impact on long term outcome on patients. Chi-Square test was used to determine the relationship between all categorical variables. For association between continuous variables and

categories Mann–Whitney U rank sum tests were used. Multivariable analyses were done using logistic regression or Cox proportional hazard regression models. The proportional hazards assumptions for all the variables were examined by testing time-dependent covariates. All p-values reported were two-sided and statistical significance was declared at $p < 0.05$. Statistical analyses were performed using SPSS software (v.19) (IBM-SPSS, Chicago, IL, USA).

Results

Two hundred seventy patients receiving SCT for NHL at our institution between January 2000 and December 2010 were included in this IRB approved analysis. Of the 270 patients, 51 patients (18.9%) underwent SCT for TL (auto-SCT=44; allo-SCT=7). The baseline characteristics are listed in Table 1.

The median age of patients at the time of transplantation was 55 years (range 33–70) and 29 (57%) were male. At diagnosis, 5 patients had stage I disease, 10 with stage II, 16 stage III and 20 patients were diagnosed with stage IV disease. Twenty four patients (47%) received 2 regimens prior to transplantation and 27 patients (53%) received three or more salvage therapies prior to transplantation. Thirty five (69%) patients were in complete remission (CR) at the time of transplantation and the rest were in partial remission. All patients had chemotherapy-sensitive disease prior to transplantation. The median stem cell dose for patients receiving auto-SCT was 3.64×10^6 CD34+ cells/ kg (range, 2.29–12.84) and 4.7×10^6 CD34+ cells/ kg (range, 2.8–10.19) for allo-SCT recipients.

Long-term outcome

The median follow up of cohort was 3 years (range 0.6–12.5). At the time of analysis, 37 patients were alive with an estimated 5 year OS and EFS rate of 61.8% and 45% respectively (Figure 1). Three year relapse rate of entire cohort was 43% and NRM of 8.5%. Three of 16 patients who were transplanted in PR had progressive disease, and rest attained a complete remission following SCT.

All long-term survivors (3 year post-SCT, n=28) were in good performance status (ECOG 0 or 1) at the time of analysis.

Risk factor analysis

Univariate analysis

Number of chemotherapy regimens pre-SCT: Several chemotherapy regimens were used after transformation to establish chemotherapy sensitivity. The most commonly used regimens include CHOP (cyclophosphamide, adriamycin, vincristine, prednisone), ESHAP (etoposide, methylprednisolone, high-dose Cytarabine, cisplatin), ICE (ifosfamide, carboplatin and, etoposide), FND (fludarabine, Mitoxantrone and dexamethasone). The number of pre-SCT chemotherapy regimens significantly influenced long-term outcome, patient receiving 3 salvage chemotherapy regimens were associated with inferior OS (5 year 38.7% vs. 86.8%, $p=0.02$) and higher NRM (2 year 16% vs. 0%, $p=0.02$). There were

trends towards inferior EFS (5 year 41.4% vs. 64.3%, $p=ns$) and increased risk of relapse (2 year 38.7% vs. 25%, $p=ns$) in patients receiving 3 regimens pre-SCT.

Early vs. Late transformation: Thirty six patients carried a diagnosis of early transformation (auto-SCT=32, allo-SCT=4) and 15 patients had late transformation (auto-SCT=12, allo-SCT=3). Patients with early transformation had superior OS (5 year 80.4% vs. 31.5%, $p=0.018$), EFS (5 year 59.3% vs. 16.2%, $p=0.027$), with a trend towards decreased risk of relapse (2 year 28.1% vs. 65.1%, $p=0.006$) and NRM (2 year 6.4% vs. 13.3%, $p=0.11$) (Figure 2).

When analyzing auto-SCT data separately, timing of transformation and numbers of pre-SCT chemotherapy regimens remained a predictive factor for outcome.

Other factors: This analysis was not meant to compare auto-SCT with allo-SCT due to limited number of patients receiving allo-SCT. However, the 5 year OS and EFS of patients receiving auto-SCT was not statistically significant compared with allo-SCT (5 year 61.8% vs. 68.5%, and 44.6% vs. 45.7%, respectively). Similarly, there was no significant difference in the rate of relapse among auto-SCT and allo-SCT recipients (2 year 38.9% vs. 33.3%). There was a trend towards higher NRM in patients receiving allo-SCT (2 year 4.6% vs. 31.4%; $p=0.06$). Age, gender, pre-SCT rituximab maintenance, stage, disease status pre-SCT (CR or PR), and conditioning regimen did not impact long-term outcome. Stem cell dose and absolute lymphocyte count on day 14 or day 28 post-SCT also had not impact on transplant outcome.

Multivariate analysis—Multivariate analysis using Cox-proportional hazard showed that early transformation was independently associated with improved overall survival (hazard ratio [HR] 3.29, 95% CI, 1.14–9.51, $p=0.028$) and event free survival (HR 2.49 95% CI, 1.1–5.6, $p=0.029$).

Correlation between numbers of regimens and timing of transformation

Not surprisingly, the timing of transformation was highly correlated with the number of regimens pre-SCT, both as continuous variable ($r^2=0.427$, $p=0.002$) and when analysis was performed using the number of regimens as a categorical variable, <3 vs. 3 regimens pre-SCT ($r^2=0.436$, $p=0.001$).

Secondary malignancies

Five patients receiving auto-SCT developed secondary malignancies. The median number of chemotherapy regimens in patients who developed secondary malignancies was 3 (range, 2–5). One patient was diagnosed with melanoma 3 years after auto-SCT. Two patients developed secondary myelodysplastic syndrome with complex karyotype 4 and 5 years post transplantation. Additional, 2 patients were diagnosed with secondary acute myeloid leukemia (AML) 5 and 6 years after transplantation. One patient with secondary AML underwent allo-SCT. At last follow up, 2 patients were alive and treated appropriately for their secondary cancer.

Discussion

In the rituximab era with maintenance strategies being widely utilized, treatment of transformed lymphoma is yet challenging as most clinical trials specifically exclude this subset of patients with what appears to be a histologically heterogeneous disease.^{1;4} The current study is unique considering one of the largest series of TL treated with SCT in the immunochemotherapy era. The outcome in this homogenous population of TL is superior compared with many previously reported case series. Rezvani et al,¹⁷ recently reported outcome of 16 patients with TL after non myeloablative conditioning regimens for allo-SCT. At 3 years, the estimated OS and PFS rates were 18% and 23%, respectively. The cumulative incidence of NRM at 3 years was 42%. In the European Group of Blood and Marrow Transplantation (EBMT) series, 50 patients who underwent high dose therapy with auto-SCT rescue for TL had 5 year OS and PFS of 51% and 30% respectively.¹⁸ Doocey et al,¹⁹ reported their outcome on 16 patients who underwent allo-SCT for TL. There were eight deaths related to complications of the transplant. Four patients died of disease relapse and the remaining four patients were alive and free of disease at < 2 years post-SCT. Recently published review article summarizes published case series of patients with TL after SCT.⁴

Our results indicate that an initial aggressive approach for early-TL may improve survival and supports our hypothesis. Patients who present with transformation at a later stage have an inferior survival even with dose intense approaches. In a French study by Ghesquieres et al,¹⁰ a matched control analysis of 60 patients with TL at diagnosis was compared with *de novo* patients with DLBCL. Among patients achieving a complete or a partial response to initial therapy, 42% and 50% of patients underwent high dose therapy followed by auto-SCT respectively. Of these 41% relapsed with low grade histology. The 5 year OS was similar between the two groups (62% vs. 57% respectively). The 5 year freedom-from-progression (FFP) rate was significantly decreased in TL compared with *de novo* DLBCL (57% vs. 33% respectively p=0.03). There are limited data comparing patients with TL at the time of diagnosis versus those with transformation that has occurred several years after a diagnosis of FL. Friedberg et al,²⁰ reported that patients who underwent a transformation within 18 months of their diagnosis of indolent lymphoma, had improved OS after auto-SCT compared with TL diagnosed after 18 months of initial diagnosis of indolent lymphoma. Patients with early transformation, receive fewer number of treatment regimens and are considered early for a transplant approach. We acknowledge the fact that patients who relapse after an SCT are treated with salvage regimens and may therefore have a survival benefit. The limitation of this study is that the patients who received SCT are a highly selected subgroup of patients with TL with chemo-sensitive disease without comparing those patients who did not undergo transplant. We however promote aggressive treatment modalities incorporating SCT upfront for TL. The focus of this discussion reflects two important future considerations: First, strategies to improve outcome following SCT and second to prevent late transformation of FL.

Radioimmunoconjugates Yttrium-90-labeled Ibritumomab tiuxetan (beta) and I-131 tositumomab (gamma) currently approved for the treatment of FL have been used in TL. Incorporating novel radioimmunotherapy as part of conditioning regimen might be an attractive option prior to NST conditioning regimen to prevent early relapse.^{21;22}

Ibritumomab-tiuxetan as part of the conditioning regimen has been added 14 days prior to an allo-SCT. This did not interfere with the engraftment kinetics and appears as an attractive strategy for patients with TL.²³

Novel alkylating agents such as bendamustine has been evaluated by Friedberg and colleagues in 15 patients.²⁴ In this study, 13 % had a CR/CRu and 53% had a partial response in patients with advanced disease. At the same time bendamustine also incorporated in auto-SCT conditioning BeEAM (bendamustine, etoposide, cytarabine, melphalan), found to be is safe and effective for resistant/ relapsed lymphoma patients, with 81% patients remained in CR after median follow-up of 18 months.²⁵ Recent data suggests histological origin of relapsed TL specifically from FL responds to immunomodulatory therapy.²⁶ Such modulation of the microenvironment needs to be considered as a post-transplant maintenance strategy. Furthermore, such therapy if considered upfront in FL may encumber transformation. The ongoing ECOG2408 study incorporates the use of these agents and though not powered to detect the rate of transformation, may provide useful insights. Finally, we recommend early referral to a transplant center to explore the most effective SCT option and enrollment in clinical trials should be encouraged.

Acknowledgments

Funding: This work was supported by National Center for Research Resources, National Institute of Health (grant # 5K-12 CA090625-09, N.R.)

Reference List

- Bernstein SH, Burack WR. The incidence, natural history, biology, and treatment of transformed lymphomas. Hematology. Am. Soc. Hematol. Educ. Program. 2009;532–541. [PubMed: 20008238]
- Al-Tourah AJ, Gill KK, Chhanabhai M, et al. Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. J. Clin Oncol. 2008; 26:5165–5169. [PubMed: 18838711]
- Clavert A, Le GS, Brissot E, et al. Reduced-intensity conditioning allogeneic stem cell transplant for relapsed or transformed aggressive B-cell non-Hodgkin lymphoma. Leuk. Lymphoma. 2010; 51:1502–1508. [PubMed: 20583964]
- Reddy N, Savani BN. Treatment options for transformed lymphoma: incorporating allogeneic stem cell transplantation in a multimodality approach. Biol. Blood Marrow Transplant. 2011; 17:1265–1272. [PubMed: 21621630]
- Hari P, Carreras J, Zhang MJ, et al. Allogeneic transplants in follicular lymphoma: higher risk of disease progression after reduced-intensity compared to myeloablative conditioning. Biol. Blood Marrow Transplant. 2008; 14:236–245. [PubMed: 18215784]
- Al-Tourah AJ, Savage KJ, Gill KK, et al. Addition of Rituximab to CHOP Chemotherapy Significantly Improves Survival of Patients with Transformed Lymphoma. ASH Annual Meeting Abstracts. 2007; 110:790.
- Davies AJ, Rohatiner AZ, Howell S, et al. Tositumomab and iodine I 131 tositumomab for recurrent indolent and transformed B-cell non-Hodgkin's lymphoma. J. Clin Oncol. 2004; 22:1469–1479. [PubMed: 15084620]
- Kaminski MS, Zelenetz AD, Press OW, et al. Pivotal study of iodine I 131 tositumomab for chemotherapy-refractory low-grade or transformed low-grade B-cell non-Hodgkin's lymphomas. J. Clin Oncol. 2001; 19:3918–3928. [PubMed: 11579112]
- Vose JM, Wahl RL, Saleh M, et al. Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. J. Clin Oncol. 2000; 18:1316–1323. [PubMed: 10715303]

10. Ghesquieres H, Berger F, Felman P, et al. Clinicopathologic characteristics and outcome of diffuse large B-cell lymphomas presenting with an associated low-grade component at diagnosis. *J. Clin Oncol.* 2006; 24:5234–5241. [PubMed: 17043351]
11. Cilley J, Winter JN. Radioimmunotherapy and autologous stem cell transplantation for the treatment of B-cell lymphomas. *Haematologica.* 2006; 91:114–120. [PubMed: 16434379]
12. Barosi G, Carella A, Lazzarino M, et al. Management of nodal indolent (non marginal-zone) non-Hodgkin's lymphomas: practice guidelines from the Italian Society of Hematology, Italian Society of Experimental Hematology and Italian Group for Bone Marrow Transplantation. *Haematologica.* 2005; 90:1236–1257. [PubMed: 16154848]
13. Eide MB, Lauritzsen GF, Kvalheim G, et al. High dose chemotherapy with autologous stem cell support for patients with histologically transformed B-cell non-Hodgkin lymphomas. A Norwegian multi centre phase II study. *Br. J. Haematol.* 2011; 152:600–610. [PubMed: 21241276]
14. Khouri IF, McLaughlin P, Saliba RM, et al. Eight-year experience with allogeneic stem cell transplantation for relapsed follicular lymphoma after nonmyeloablative conditioning with fludarabine, cyclophosphamide, and rituximab. *Blood.* 2008; 111:5530–5536. [PubMed: 18411419]
15. Barrett AJ, Savani BN. Stem cell transplantation with reduced-intensity conditioning regimens: a review of ten years experience with new transplant concepts and new therapeutic agents. *Leukemia.* 2006; 20:1661–1672. [PubMed: 16871277]
16. Gine E, Montoto S, Bosch F, et al. The Follicular Lymphoma International Prognostic Index (FLIPI) and the histological subtype are the most important factors to predict histological transformation in follicular lymphoma. *Ann. Oncol.* 2006; 17:1539–1545. [PubMed: 16940035]
17. Rezvani AR, Storer B, Maris M, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in relapsed, refractory, and transformed indolent non-Hodgkin's lymphoma. *J. Clin Oncol.* 2008; 26:211–217. [PubMed: 18056679]
18. Williams CD, Harrison CN, Lister TA, et al. High-dose therapy and autologous stem-cell support for chemosensitive transformed low-grade follicular non-Hodgkin's lymphoma: a case-matched study from the European Bone Marrow Transplant Registry. *J. Clin Oncol.* 2001; 19:727–735. [PubMed: 11157024]
19. Doocey RT, Toze CL, Connors JM, et al. Allogeneic haematopoietic stem-cell transplantation for relapsed and refractory aggressive histology non-Hodgkin lymphoma. *Br. J. Haematol.* 2005; 131:223–230. [PubMed: 16197454]
20. Friedberg JW, Freedman AS. High-dose therapy and stem cell transplantation in follicular lymphoma. *Ann. Hematol.* 1999; 78:203–211. [PubMed: 10391100]
21. Gopal AK, Pagel JM, Rajendran JG, et al. Improving the efficacy of reduced intensity allogeneic transplantation for lymphoma using radioimmunotherapy. *Biol Blood Marrow Transplant.* 2006; 12:697–702. [PubMed: 16785058]
22. Khouri IF, Saliba RM, Hosing C, et al. Efficacy and Safety of Yttrium 90 (90Y) Ibritumomab Tiuxetan in Autologous and Nonmyeloablative Stem Cell Transplantation (NST) for Relapsed Non-Hodgkin's Lymphoma (NHL). *ASH Annual Meeting Abstracts.* 2006; 108:315.
23. Fietz T, Uharek L, Gentilini C, et al. Allogeneic hematopoietic cell transplantation following conditioning with 90Y-ibritumomab-tiuxetan. *Leuk. Lymphoma.* 2006; 47:59–63. [PubMed: 16321828]
24. Friedberg JW, Cohen P, Chen L, et al. Bendamustine in patients with rituximab-refractory indolent and transformed non-Hodgkin's lymphoma: results from a phase II multicenter, single-agent study. *J. Clin Oncol.* 2008; 26:204–210. [PubMed: 18182663]
25. Visani G, Malerba L, Stefani PM, et al. BeEAM (bendamustine, etoposide, cytarabine, melphalan) before autologous stem cell transplantation is safe and effective for resistant/relapsed lymphoma patients. *Blood.* 2011; 118:3419–3425. [PubMed: 21816830]
26. Czuczman MS, Vose JM, Witzig TE, et al. The differential effect of lenalidomide monotherapy in patients with relapsed or refractory transformed non-Hodgkin lymphoma of distinct histological origin. *Br. J. Haematol.* 2011; 154:477–481. [PubMed: 21707581]

Clinical Practice Points

- Transformed non-Hodgkin's lymphoma (TL) arising from follicular lymphoma carries a poor prognosis with a median survival after transformation being less than a year
- Several studies evaluating the role of autologous stem cell transplantation (auto-SCT) as a salvage regimen have been reported and a subset of patients benefit from this modality of treatment
- With an improvement in supportive care, outcome after allogeneic stem cell transplantation (allo-SCT) has been improved significantly over past decades, however, very limited data is available in TL
- In the era of emerging novel therapies, the actual timing, optimal conditioning regimens and long term impact of the type of stem cell transplantation (auto-SCT vs. allo-SCT) is unclear
- Our results indicate that an initial aggressive approach for early-TL may improve survival. Patients who present with transformation at a later stage have an inferior survival even with dose intense approaches
- In the rituximab era with maintenance strategies being widely utilized, treatment of TL is yet challenging as most clinical trials specifically exclude this subset of patients with what appears to be a histologically heterogeneous disease
- The current study is unique considering one of the largest series of TL treated with SCT in the immunochemotherapy era
- This study highlights the importance of early referral for transplantation
- Larger studies need to be performed, including analysis of registry data to evaluate the outcome of TL in the rituximab era after SCT (auto or allo). We also recommend clinical trial participation for this rare disease

Figure 1.
(a) Overall survival (OS); and (b) event free survival (EFS) of all patients with transformed lymphoma

Figure 2.
Long term survival of patients with early vs. late transformation (TL): (a) overall survival;
and (b) event free survival.

Table 1

Baseline characteristics

Patients	N= 51 pts
Sex (male)	29 (57%)
Age (median)	55 yrs (33–70)
Stage	
I and II	15 (29.4%)
III and IV	36 (70.6%)
Transformation	
At diagnosis or within a year	36 (71%)
>1 year	15 (29%)
Number of extranodal sites	
0–1	47
2	4
Median no of regimens prior to SCT	3(2–5)
2	24 (47%)
3 or more	27 (53%)
Disease status prior to SCT	
CR	35 (69%)
*PR	16 (31%)
Type of Transplantation	
Auto- SCT	44 (86%) (32 in CR /12 in PR)
Allo-SCT	7 (14%) (3 in CR/4 in PR)
RIC	4
Myeloablative	3
Conditioning Regimen	
CBV	45 (88%)
FCR	2 (4%)
TBI based	4 (8%)
Median stem cell dose	
Auto-SCT	3.64×10 ⁶ CD34/kg (2.29–12.84)
Allo-SCT	4.70×10 ⁶ CD34/kg (2.8–10.19)

CR: Complete remission, PR: Partial Remission, Auto-SCT: autologous ; Allo-SCT: allogeneic stem cell transplantation, RIC: reduced intensity conditioning, MRD- Matched related donor MUD: matched unrelated donor, CBV: cyclophosphamide, BCNU and etoposide; FCR: Fludarabine, Cyclophosphamide and rituximab ; TBI: Total body Irradiation;

* 4 received allo-SCT.