Published in final edited form as:
Biol Blood Marrow Transplant. 2011 September ; 17(9): 1265–1272. doi:10.1016/j.bbmt.2011.05.002.

Treatment Options for Transformed Lymphoma: Incorporating Allogeneic Stem Cell Transplantation in a Multimodality Approach

Nishitha Reddy 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 (TL) arising from follicular lymphoma carries a poor prognosis and the median survival time after transformation is approximately 10-12 months. Standard chemotherapy and radioimmunotherapy have offered promising responses however; the duration of response does not appear to last long. 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 are 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. This review addresses the approaches to the management of patients with TL.

Keywords

Transformed lymphoma; autologous stem cell transplant; allogeneic stem cell transplant; radioimmunotherapy

Introduction

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 is referred to as transformed lymphoma (TL). Progression from FL grade 1 or 2 to FL grade 3 is not considered as transformation; progression from FL grade 3 to a frank DLBCL is often considered TL.[1;2] Occasionally, there is a synchronous presentation of diffuse large cell with a follicular component in the lymph node specimen or a metachronous presentation of an aggressive lymphoma in one lymph node and a low grade component at a distant site.[1] The

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

incidence varies from 17%-70%. Most of these studies were conducted in the pre-rituximab era; the true incidence of transformation in the era of monoclonal antibody therapy is unknown. The prognosis for TL is generally poor with rapid progression of the disease. The median survival after transformation is about one year thus accounting for higher proportion of deaths in patients with follicular lymphoma (FL). The Follicular Lymphoma International Prognostic Index and the histological subtype (grade 3) are important predictors of transformation in FL.[2]

Disease-free survival (DFS) in TL treated with standard chemotherapy is shorter compared with de novo DLBCL. Young patients with limited stage chemo-sensitive disease experience prolonged survival. This group however, accounts for <20% of all TL. High overall response rates, ranging from 50% to 80%, with an acceptable safety were reported in patients who were treated with ibritumomab, tositumomab, or rituximab therapy.[6]

There is paucity of literature on the treatment of TL and therefore deciding on the optimal evidence based treatment is a challenge. We are unaware of any prospective trials exclusively for TL. The most specific publications report on auto-SCT showed encouraging results.[7] However, these series are highly selected groups of patients and unfortunately, the majority of patients with TL are likely to be too old, with poor performance status or have had an insufficient response to re-induction chemotherapy and making them ineligible for SCT. Successful results have been reported in selected patient populations who have achieved long-term DFS after allo-SCT. Interpretations of these data are limited by small sample sizes and study patients spanned over 1-2 decades. Non allo-SCT treatment options are limited by high relapse rate and short DFS. Allo-SCT is safer than ever before and it is possible that novel immunomodulatory reduced intensity conditioning regimen (RIC) might provide high cure rate in this otherwise fatal lymphoid malignancy.

In this review we discuss the available treatment modalities and their incorporation into management to improve outcome in patients with transformation of follicular lymphoma to diffuse large B-cell lymphoma.

Biological mechanism of transformation

The underlying biology of transformation is not fully understood. Gene expression profiling of 20 paired samples of FL and TL performed by Davies et al.,[8] noted two pathways by which TL may evolve. One is via similar proliferation rate as that of the preceding FL and the other set over-expressed genes associated with proliferation signatures suggesting that an acquired high proliferation rate underlies transformation. The acquisition of novel mutations via somatic hyper mutations has also been implicated in the pathogenesis of TL.[8-12] Importantly it has been suggested that the tumor microenvironment may play a crucial role in transformation. In a study by Glas et al., gene expression profiling (GEP) signatures were performed on FL samples of patients who later had transformation or had no subsequent transformation. The GEP of patient samples who did not transform had a down regulation of the immune related genes therefore implying that the transformation may be mediated by an “immune signature”. There was also an over expression of CD69 which is an activated T cell marker in samples that were destined to transform.[13] Also, perifollicular localization of T-regs, number of T-regs and T cells expressing low numbers of programmed cell death-1 protein were associated with increased risk of transformation.[14-16] The exact mechanism as to how the microenvironment contributes to transformation has not been studied.

Outcome of early vs. late transformation

In most cases the transformation occurs in patients with a history of indolent lymphoma. Likewise, histological transformation may be the first manifestation of lymphoma without a

prior history of indolent lymphoma. Compared with de novo DLBCL, TL at diagnosis has similar overall survival (OS) but lower complete response rates to initial therapy and more than half of these patients have continuous risk of indolent relapse. At time of indolent relapse, salvage treatment elicits new objective response in about half of the cases eventually accounting for the similar OS of TL and DLBCL.

In a French study, 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).[17] It is possible that high dose chemotherapy upfront in patients with TL improved the FFP and OS rates. There are no studies 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., 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.[18]

In the absence of a clinical trial, we can extrapolate from limited available evidence (and our experience) that patients with TL at the time of diagnosis (or early TL) have a better prognosis compared with patients who present with transformation several years later. This group may therefore be considered for an aggressive approach including allo-SCT incorporating radioimmunotherapy as a part of conditioning regimen or its use in pre-transplantation period to prevent early relapses after SCT, a major cause of treatment failure.

Treatment modalities in transformed lymphoma

The overall outcome for patients with TL without SCT in most series is poor, with most deaths attributed to lymphoma. Age, response to salvage therapy, B symptoms, lactate dehydrogenase values, bone marrow involvement, stage, no prior chemotherapy, and early transformation were all predictive factors for survival after transformation.[19]

Principle goal in the management of TL in our view is to consider combined modality treatment to increase CR rate followed by whenever possible consolidative therapy of curative intent with SCT, preferably RIC allo-SCT (reducing the risk of indolent relapse) in eligible patients (discussed below).

Chemotherapy and external beam radiation therapy in TL

Several combination chemotherapeutic agents have shown early responses in patients with TL. These chemotherapeutic agents have however not shown a major improvement in continued responses, majority patients will ultimately relapse and pose a challenge in retreatment.

In patients with TL who have not been exposed to an anthracycline based regimen, rituximab-CHOP therapy should be considered. This is based on the outcome of patients with de novo DLBCL. The addition of rituximab to chemotherapy improved the outcome of patients with TL.[20]

Novel alkylating agents such as bendamustine has been evaluated by Friedberg and colleagues in 15 patients. In this study, 13 % had a CR/CRu and 53% had a partial response. The median duration of response was 2.3 months.[21] There are no recommendations based on

evidence regarding the optimal therapy at the time of transformation. A major reason for this is due to the lack of inclusion of patients with TL in clinical trials.

With the use of PET scans and its role in TL, one may truly isolate patients with localized site of transformation.[22] A Stanford study by Yeun et al., reported that involved field radiation therapy (IFRT) might benefit patients with isolated nodal area of transformation.[23]

Radioimmunotherapy in TL

Lymphomas are extremely sensitive to radiation therapy. Monoclonal antibodies targeting the B cells have clearly improved the OS. When anti-CD20 antibodies bind to surface antigens, they induce apoptosis, antibody-dependent cellular cytotoxicity, and complement-dependent cellular cytotoxicity of lymphoma cells.[24;25] More recently progress has been made in the development of radioimmunotherapy with anti-CD20 antibodies. The unique features of radioimmunotherapy include the delivery of radiation to the tumor bed and exert their direct and indirect cytotoxic effects.

Therapy with radio-immunoconjugates has undergone extensive clinical testing using murine anti-CD20MAb conjugated to either iodine-131 or Yttrium-90. Two radioimmunoconjugates Yttrium-90-labeled ibritumomab tiuxetan (beta) and I-131 tositumomab (gamma) are currently approved for the treatment of FL and have been used in TL. Tositumomab has also been approved for TL

A phase III randomized study compared Y-90 ibritumomab tiuxetan with rituximab in 143 patients with relapsed, refractory, follicular or transformed lymphoma. Patients received either a single intravenous (IV) dose of Y-90 ibritumomab tiuxetan 0.4 mCi/kg or rituximab 375 mg/m2 IV weekly for four doses. The radioimmunotherapy group was pretreated with two rituximab doses (250 mg/m2) to improve biodistribution and one dose of indium-111 ibritumomab tiuxetan for imaging and dosimetry. Of the 13 patients with TL, 9 patients received radioimmunotherapy. The overall response rate was 56% (5 of nine patients) versus 75% in the rituximab control arm.[26]

An open label phase II study was conducted to establish the efficacy and safety of I-131 tositumomab in recurrent TL. A single dosimetric dose was followed at 7 to 14 days by the patient-specific administered radioactivity required to deliver a total body dose of 0.75 Gy. A response rate in patients with TL was 71%. At the time this trial was reported, in patients who attained a CR or CRu the median duration of response was not reached.[27]

An integrated efficacy analysis of the five clinical trials of tositumomab and iodine-131 tositumomab in patients with relapsed or refractory low-grade, FL or TL led to the regulatory approval of the iodine-131 tositumomab. In this report by Fisher et al, evaluating the role of I-131 tositumomab among 250 patients in five different clinical trials with TL, suggests a potential role in a subset of patients.[28-31] Seventy one patients (28%) were diagnosed with TL. Of the 81 patients with time to progression > 12 months, 23% had TL.[32]

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 attractive as a strategy for patients with relapsed TL.[33]

Auto-SCT in TL

High dose therapy followed by auto-SCT has shown to improve both DFS and OS for patients with relapsed low or intermediate grade lymphoma.[34-36] This approach has therefore been investigated in patients with TL; however the data supporting the efficacy of this approach for patients with TL are limited, as most studies include only small numbers of

patients over a decade and the median follow-up of patients in these studies are quite variable. Table 1 summarizes the results of auto-SCT in TL. Friedberg et al, reported their results on 27 patients who underwent auto-SCT for TL. Patients who had a transformation within six months of their diagnosis were excluded from this study. Eleven of the 27 patients experienced a relapse and four patients developed myelodysplasia or secondary acute myeloid leukemia. Twelve patients continued to be in complete remission at 36 months.[18]

In another study, analyzing 35 patients who underwent auto-SCT for TL, the five year overall survival (OS) and progression free survival (PFS) was 37% and 36%. At a median follow up of 52 months, 26% died due to progressive disease, and 8% developed myelodysplasia. In the multivariate analysis, Chen et al were able to identify only advanced age as a predictor of survival. The median duration from diagnosis to transformation was 3.6 years in this study.[37] Several other studies have presented similar results with an auto-SCT in TL [38;39] (Table 1).

The benefit of graft purging remains unproven and has not been practiced except in clinical trials. In a long term follow up study Kasamon et al., report phase II results of 12 patients with TL who underwent auto-SCT with 4-hydroperoxycyclophosphamide (4-HC) purging as part of initial or salvage therapy. Autologous grafts derived from bone marrow harvest were treated ex-vivo with 4-HC and cryopreserved until infusion. The preparative regimen consisted of cyclophosphamide and total body irradiation (1200 cGy, TBI) or busulfan and cyclophosphamide. At a median follow up of 16.6 years, only 3 were event free. Two had non-relapse death and the remaining 7 patients died of lymphoma at 0.1-4.3 years after BMT. Despite the fact that at 10 years the OS was 50%, results should be interpreted with caution considering small study population and probably highly selected group. Similarly, the role of purging remains controversial in the rituximab era.[40] A report by Andreadis et al., using purged or unpurged cells for auto-SCT in 22 patients with TL showed, among patients who achieved CR prior to transplant; the rates of DFS, EFS and OS at 5 years were 52, 44 and 80% respectively. In univariable and multivariable analysis, achievement of CR was associated with improved outcome after auto-SCT.[41] Similar results were observed by the Ohio state group who reported their 3 year PFS and OS rate of 40% and 52% respectively in 24 patients with TL after auto-SCT. The difference in outcome might be due to inclusion of patients with minimal disease state at the time of transplantation.[42]

Foran et al. also showed a 5 year OS and PFS in the range of 50% in patients younger than 60 years at a median follow up of 2.4 years. The median time to transformation was 6 months.[43] 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. The median time to transformation from diagnosis was 3 years. Three patients developed secondary malignancies.[44] Schouten et al., reported their results of 10 patients undergoing auto-SCT for TL in the 1980's. They report a median overall survival of 2 months with 70% procedure related deaths.[45] Again, interpretation of data is limited by small studies and variable transplant periods- spanned over 5-15 years, and include patients both in the pre and post- rituximab era.

To summarize, auto-SCT appears to play a role in patients who present with de novo TL and appear to be beneficial as a consolidative therapy for patients with extensive stage disease in first complete remission.[46] Allo-SCT options should be weighed against auto-SCT in patients with suitable donor, especially in patients who have received multiple prior regimens and have had a long history of FL. Auto-SCT may not be the best approach considering very high relapse rate in this group. Therefore, tandem auto-SCT followed by safer non-ablative allo-SCT is also pursued to maintain remission.

Time to consider early allogeneic stem cell transplantation in TL

With increasing use of RIC regimens, many older patients are able to receive allo-SCT as curative intent. The hypothesis that RIC transplants could be used to deliver an effective graft-versus-lymphoma (GVL) effect is true. Indeed, the typical delayed regression of malignant disease, long after any effect from the preparative regimen has passed, is proof of principle that RIC transplants exert strong and curative alloresponses against the recipient's malignancy.[47;48]

Given the high relapse rate seen even after auto-SCT, and the potential benefit of a GVL after allo-SCT, many more eligible patients with NHL including TL are receiving allo-SCT (Table 2). The intrinsic difficulty of interpreting the wide variation among study individual reports lies with the heterogeneity of the studies (single-center vs. multicenter, lack of larger prospective data), the heterogeneity of the patients studied (in particular, whether only patients with TL were included), the variation in the RIC transplant procedure itself (e.g., the conditioning regimen, GVHD prophylaxis, and stem cell source), and the duration of follow-up.

Doocey et al., 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.[49] The significant number of deaths may have been related to an increased amount of prior therapy. Therefore, it is important to optimally time the allo-SCT rather than waiting for inevitable disease relapse. In another study by Rezvani et al., sixteen patients with TL underwent RIC allo-SCT at a median age of 54 years. Patients had either unrelated or related donor's stem cell sources and the median numbers of regimens were six. On a univariate analysis, increased mortality was associated with patients who had TL. The cumulative incidence of non-relapse-mortality (NRM) at 3 years was 42%. These patients also experienced a high relapsed rate with a median time to progression of 1.6 months. The 3-year PFS and OS were 18% and 21% respectively.[50]

Clavert et al, reported data on RIC allo-SCT in relapsed aggressive B cell lymphoma in an attempt to reduce TRM, 15 of 19 patients had TL. Of the entire group, 3 patients were documented with disease progression while four were not evaluable due to early death. In the auto-allo-SCT tandem approach the overall survival at 4 years was 70%. In the auto-SCT followed by allo-SCT non-tandem approach, the overall survival was 66% at 4 years.[51] In this study it is possible that auto-SCT provided the tumor control initially until the immune GVL took effect. In another report by Thomson et al, RIC allo-SCT among 18 patients, the 4 year OS was 60%. In this study, six of the seven relapse events occurred in the first 10 months of RIC allo-SCT.[52]

Hamadani et al., discussed the role of allo-SCT for patients with relapsed chemorefractory aggressive B-cell lymphoma. Among 5 patients with TL four had stable disease and one patient had progressive disease at the time of transplant, the 5 year OS was reported to be 100%. It is however noteworthy that albeit a small number, a group of chemorefractory patients can be salvaged with a allo-SCT.[53-55]

Historically, limitation of allo-SCT has been TRM. In order to offer the curative allo-SCT treatment option in most patients, safer regimens with acceptable GVHD associated morbidity and TRM are preferred. Among several RIC regimens fludarabine, cyclophosphamide and rituximab (FCR), a non-ablative conditioning regimen followed by either related or unrelated donor allo-SCT has been reported to be very safe and effective in B-cell lymphoid malignances. A recently published MDACC study showed excellent OS

and OS (85% and 83%, respectively after median follow-up of 60 months) for relapsed FL after FCR RIC allo-SCT. The incidence of grade II-IV acute GVHD was only 11%.[56]

We have also observed safety of FCR regimen at our institution in patients with B-cell NHL with minimal GVHD and TRM compared to other RIC regimens. In addition to benefits of decreasing risk of GVHD and better disease control in patients with B-cell malignancies, one would expect lower EBV reactivation and post transplant lymphoproliferative disorders after this regimen.[57;58] There is an almost universal consensus, that chemosensitivity and disease control before allo-SCT is utmost important to prevent early relapse which is a major cause of treatment failure in TL. Incorporating novel radioimmunotherapy as part of conditioning regimen might be very attractive option prior to non-ablative FCR conditioning regimen to prevent early relapse. In this era, a stem cell source can be found for virtually all patients who have an indication to receive allo-SCT. RIC haploidentical-related donor or cord blood transplantations (CBT) have emerged as alternatives to fill the gap for those patients who do not have matched related donor (MRD) or unrelated donor (URD) and the outcome of these types of transplantations are expected to be better than chemotherapy alone or even better than auto-SCT for selected high risk heavily pre-treated TL. The individual transplant center experience using URD, CBT, and haploidentical transplantation should also be taken into consideration. Enrollment in clinical trials should be encouraged.

Pre-transplantation radioimmunotherapy

Radioimmunotherapy has been integrated with in transplant conditioning regimen.[59] The maximally tolerated dose of single agent 131I-tositumomab followed by auto-SCT was found to be 27 Gy to the critical normal organ receiving the greatest radiation. Cardiopulmonary toxicity was noted at higher doses. This strategy helped deliver 10 times the radiation dose as would the whole body and twice the radiation dose as would the critical organs such as the lungs. With this approach the non-hematopoietic toxicities were low. The overall response rate was 95% with 84% complete responses.[60] In a multivariable cohort analysis of 125 patients, in relapsed refractory FL, myeloablative 131I-tositumomab followed by ASCT was compared with conventional high-dose therapy followed by auto-SCT. The 5-year PFS was 48% for the high-dose radioimmunotherapy group and 29% for the high-dose therapy by auto-SCT group (P = .03). Interestingly, there was no evidence of increased myelodysplastic syndrome at an 8 year follow up.[61]

Other investigators have evaluated the use of escalating the dose of 90Y-ibritumomab tiuxetan in combination with chemotherapy and auto-SCT. Winter et al escalated the dose of Zevalin beyond 0.5 mCi/kg along with high-dose carmustine (BCNU), etoposide, cytarabine, and melphalan (BEAM regimen) and auto-SCT and found 3-year PFS and OS rates of 43% and 63%, respectively, in a heavily pretreated group of 33 patients with relapsed and refractory lymphoma.[62]

Vose et al., evaluated radioimmunotherapy in a phase II trial among 40 patients with DLBCL. 0.75 Gy whole-body dose of Bexxar was administered 7 days prior to initiating full-dose BEAM chemotherapy and 12 days prior to auto-SCT with no appreciable increase in toxicities. This regimen yielded an estimated 3-year PFS of 70% and OS of 81%.[63]

For patients in whom a non-ablative transplant is preferred, radioimmunotherapy can be employed to provide cytoreduction to safely induce disease control while minimizing non-hematologic toxicity. The allo-SCT could maintain the remissions via the GVL effect, and reconstitute hematopoiesis.[36] Using this approach, 16 patients with relapsed CD20+ Lymphoma, of which 15 patients were chemotherapy resistant, underwent therapy with 0.4 mCi/kg Y-90 ibritumomab tiuxetan followed by fludarabine and 2 Gy TBI and matched allo-SCT. At day 28, seven of 16 patients demonstrated responses.[64] Khouri et al., reported

a feasibility study using escalated doses of 90Y-ibritumomab tiuxetan prior to cyclophosphamide, fludarabine, rituximab, and allo-SCT in seven patients with relapsed B-cell NHL.[65] Though, longer follow up on outcome and toxicities are needed, it is clear that such approaches need to be urgently considered for TL.

Summary

Patients with early TL appear to have a better prognosis than late TL. Several factors may affect the natural history of FL that undergoes transformation. It would be of interest to be able to identify patients based on either the tumor microenvironment or their gene expression profiling, as to patients who are destined to undergo transformation. Multiple treatment approaches, resistance mechanisms inherent to the tumor, alteration of the tumor microenvironment may play a role in such transformation. In the rituximab era, with the increased use of maintenance strategies, the true incidence of such transformation is unknown. In the PET era, it is possible that transformation to an aggressive phenotype is identified early along with the clinical features that are suggestive of transformation and therefore affect prognosis and early treatment decisions. Novel targeted agents currently in clinical trials may change the treatment paradigm in the future.

Treatment modality with radioimmunotherapy appears promising however response duration is short lived. We believe prior radioimmunotherapy or incorporating it as a part of RIC allo-SCT might be an attractive option to prevent early relapse before graft-versus-lymphoma takes over disease control. Allo-SCT should be considered early for those patients who have received 2 or more therapies including an anthracycline for FL, when a related or an unrelated donor is available. Alternate stem cell source using CB or haploidentical related donor also needs to be considered. Tandem auto followed by allo-SCT needs to be explored in selected patients with early good results in a small series.

Considering limited data available in patients with TL, larger studies are needed. This should include analysis of registry data to the evaluate outcome of TL in the rituximab era after SCT (auto or allo). We also recommend early referral to a transplant center to explore the most effective SCT option and if available to be enrolled in a clinical trial.

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

1. 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]
2. 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]
3. 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]
4. Bastion Y, Sebban C, Berger F, et al. Incidence, predictive factors, and outcome of lymphoma transformation in follicular lymphoma patients. J.Clin Oncol. 1997; 15:1587–1594. [PubMed: 9193357]
5. Garvin AJ, Simon RM, Osborne CK, et al. An autopsy study of histologic progression in non-Hodgkin's lymphomas. 192 cases from the National Cancer Institute. Cancer. 1983; 52:393–398. [PubMed: 6344979]

6. Ahmed S, Winter JN, Gordon LI, Evens AM. Radioimmunotherapy for the treatment of non-Hodgkin lymphoma: current status and future applications. Leuk.Lymphoma. 2010; 51:1163–1177. [PubMed: 20470217]
7. Oliansky DM, Gordon LI, King J, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of follicular lymphoma: an evidence-based review. Biol Blood Marrow Transplant. 2010; 16:443–468. [PubMed: 20114084]
8. Davies AJ, Rosenwald A, Wright G, et al. Transformation of follicular lymphoma to diffuse large B-cell lymphoma proceeds by distinct oncogenic mechanisms. Br.J.Haematol. 2007; 136:286–293. [PubMed: 17278262]
9. Carlotti E, Wrench D, Matthews J, et al. Transformation of follicular lymphoma to diffuse large B-cell lymphoma may occur by divergent evolution from a common progenitor cell or by direct evolution from the follicular lymphoma clone. Blood. 2009; 113:3553–3557. [PubMed: 19202129]
10. Rossi D, Berra E, Cerri M, et al. Aberrant somatic hypermutation in transformation of follicular lymphoma and chronic lymphocytic leukemia to diffuse large B-cell lymphoma. Haematologica. 2006; 91:1405–1409. [PubMed: 17018394]
11. Lawrie CH, Chi J, Taylor S, et al. Expression of microRNAs in diffuse large B cell lymphoma is associated with immunophenotype, survival and transformation from follicular lymphoma. J.Cell Mol.Med. 2009; 13:1248–1260. [PubMed: 19413891]
12. Martinez-Climent JA, Alizadeh AA, Segraves R, et al. Transformation of follicular lymphoma to diffuse large cell lymphoma is associated with a heterogeneous set of DNA copy number and gene expression alterations. Blood. 2003; 101:3109–3117. [PubMed: 12406872]
13. Glas AM, Knoops L, Delahaye L, et al. Gene-expression and immunohistochemical study of specific T-cell subsets and accessory cell types in the transformation and prognosis of follicular lymphoma. J.Clin Oncol. 2007; 25:390–398. [PubMed: 17200149]
14. Farinha P, Al-Tourah A, Gill K, et al. The architectural pattern of FOXP3-positive T cells in follicular lymphoma is an independent predictor of survival and histologic transformation. Blood. 2010; 115:289–295. [PubMed: 19901260]
15. Carreras J, Lopez-Guillermo A, Fox BC, et al. High numbers of tumor-infiltrating FOXP3-positive regulatory T cells are associated with improved overall survival in follicular lymphoma. Blood. 2006; 108:2957–2964. [PubMed: 16825494]
16. Carreras J, Lopez-Guillermo A, Roncador G, et al. High numbers of tumor-infiltrating programmed cell death 1-positive regulatory lymphocytes are associated with improved overall survival in follicular lymphoma. J.Clin Oncol. 2009; 27:1470–1476. [PubMed: 19224853]
17. 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]
18. Friedberg JW, Freedman AS. High-dose therapy and stem cell transplantation in follicular lymphoma. Ann.Hematol. 1999; 78:203–211. [PubMed: 10391100]
19. 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]
20. 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.
21. 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]
22. Noy A, Schoder H, Gonen M, et al. The majority of transformed lymphomas have high standardized uptake values (SUVs) on positron emission tomography (PET) scanning similar to diffuse large B-cell lymphoma (DLBCL). Ann.Oncol. 2009; 20:508–512. [PubMed: 19139176]
23. Yuen AR, Kamel OW, Halpern J, Horning SJ. Long-term survival after histologic transformation of low-grade follicular lymphoma. J.Clin Oncol. 1995; 13:1726–1733. [PubMed: 7602362]

24. Buchsbaum DJ, Wahl RL, Normolle DP, Kaminski MS. Therapy with unlabeled and 131I-labeled pan-B-cell monoclonal antibodies in nude mice bearing Raji Burkitt's lymphoma xenografts. Cancer Res. 1992; 52:6476–6481. [PubMed: 1423295]
25. Golay J, Zaffaroni L, Vaccari T, et al. Biologic response of B lymphoma cells to anti-CD20 monoclonal antibody rituximab in vitro: CD55 and CD59 regulate complement-mediated cell lysis. Blood. 2000; 95:3900–3908. [PubMed: 10845926]
26. Witzig TE, Flinn IW, Gordon LI, et al. Treatment with ibritumomab tiuxetan radioimmunotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. J.Clin Oncol. 2002; 20:3262–3269. [PubMed: 12149300]
27. 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]
28. 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]
29. 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]
30. Horning SJ, Younes A, Jain V, et al. Efficacy and safety of tositumomab and iodine-131 tositumomab (Bexxar) in B-cell lymphoma, progressive after rituximab. J.Clin Oncol. 2005; 23:712–719. [PubMed: 15613695]
31. Kaminski MS, Estes J, Zasadny KR, et al. Radioimmunotherapy with iodine (131)I tositumomab for relapsed or refractory B-cell non-Hodgkin lymphoma: updated results and long-term follow-up of the University of Michigan experience. Blood. 2000; 96:1259–1266. [PubMed: 10942366]
32. Fisher RI, Kaminski MS, Wahl RL, et al. Tositumomab and iodine-131 tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. J.Clin Oncol. 2005; 23:7565–7573. [PubMed: 16186600]
33. 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]
34. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N.Engl.J.Med. 1995; 333:1540–1545. [PubMed: 7477169]
35. Laudi N, Arora M, Burns LJ, et al. Long-term follow-up after autologous hematopoietic stem cell transplantation for low-grade non-Hodgkin lymphoma. Biol Blood Marrow Transplant. 2005; 11:129–135. [PubMed: 15682074]
36. Laport GG. The role of hematopoietic cell transplantation for follicular non-Hodgkin's lymphoma. Biol Blood Marrow Transplant. 2006; 12:59–65. [PubMed: 16399587]
37. Chen CI, Crump M, Tsang R, Stewart AK, Keating A. Autotransplants for histologically transformed follicular non-Hodgkin's lymphoma. Br.J.Haematol. 2001; 113:202–208. [PubMed: 11328303]
38. Sabloff M, Atkins HL, ce-Bruckler I, et al. A 15-year analysis of early and late autologous hematopoietic stem cell transplant in relapsed, aggressive, transformed, and nontransformed follicular lymphoma. Biol Blood Marrow Transplant. 2007; 13:956–964. [PubMed: 17640600]
39. Smith SD, Bolwell BJ, Advani AS, et al. High rate of survival in transformed lymphoma after autologous stem cell transplant: pathologic analysis and comparison with de novo diffuse large B-cell lymphoma. Leuk.Lymphoma. 2009; 50:1625–1631. [PubMed: 19672775]
40. Kasamon YL, Jones RJ, Gocke CD, et al. Extended follow-up of autologous bone marrow transplantation with 4-hydroperoxycyclophosphamide (4-HC) purging for indolent or transformed non-Hodgkin lymphomas. Biol Blood Marrow Transplant. 2011; 17:365–373. [PubMed: 20655387]
41. Andreadis C, Schuster SJ, Chong EA, et al. Long-term event-free survivors after high-dose therapy and autologous stem-cell transplantation for low-grade follicular lymphoma. Bone Marrow Transplant. 2005; 36:955–961. [PubMed: 16205727]

42. Hamadani M, Benson DM Jr. Lin TS, et al. High-dose therapy and autologous stem cell transplantation for follicular lymphoma undergoing transformation to diffuse large B-cell lymphoma. Eur.J.Haematol. 2008; 81:425–431. [PubMed: 18774954]
43. Foran JM, Apostolidis J, Papamichael D, et al. High-dose therapy with autologous haematopoietic support in patients with transformed follicular lymphoma: a study of 27 patients from a single centre. Ann.Oncol. 1998; 9:865–869. [PubMed: 9789609]
44. 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]
45. Schouten HC, Bierman PJ, Vaughan WP, et al. Autologous bone marrow transplantation in follicular non-Hodgkin's lymphoma before and after histologic transformation. Blood. 1989; 74:2579–2584. [PubMed: 2804380]
46. Dilhuydy MS, Lamy T, Foussard C, et al. Front-line high-dose chemotherapy with rituximab showed excellent long-term survival in adults with aggressive large b-cell lymphoma: final results of a Phase II GOELAMS Study. Biol Blood Marrow Transplant. 2010; 16:672–677. [PubMed: 20045738]
47. 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]
48. Shea T, Johnson J, Westervelt P, et al. Reduced-Intensity Allogeneic Transplantation Provides High Event-Free and Overall Survival in Patients with Advanced Indolent B Cell Malignancies: CALGB 109901. Biol Blood Marrow Transplant. 2011
49. 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]
50. 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]
51. 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]
52. Thomson KJ, Morris EC, Bloor A, et al. Favorable long-term survival after reduced-intensity allogeneic transplantation for multiple-relapse aggressive non-Hodgkin's lymphoma. J.Clin Oncol. 2009; 27:426–432. [PubMed: 19064981]
53. Hamadani M, Benson DM Jr. Hofmeister CC, et al. Allogeneic stem cell transplantation for patients with relapsed chemorefractory aggressive non-hodgkin lymphomas. Biol Blood Marrow Transplant. 2009; 15:547–553. [PubMed: 19361746]
54. Ramadan KM, Connors JM, Al-Tourah AJ, et al. Allogeneic SCT for relapsed composite and transformed lymphoma using related and unrelated donors: long-term results. Bone Marrow Transplant. 2008; 42:601–608. [PubMed: 18695664]
55. Hamadani M, Awan FT, Elder P, et al. Feasibility of allogeneic hematopoietic stem cell transplantation for follicular lymphoma undergoing transformation to diffuse large B-cell lymphoma. Leuk.Lymphoma. 2008; 49:1893–1898. [PubMed: 18949613]
56. 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]
57. Reddy N, Rezvani K, Barrett AJ, Savani BN. Strategies to prevent EBV reactivation and post-transplant lymphoproliferative disorders (PTLD) after allogeneic stem cell transplantation in high risk patients. Biol Blood Marrow Transplant. 2010
58. Savani BN, Pohlmann PR, Jagasia M, et al. Does peritransplantation use of rituximab reduce the risk of EBV reactivation and PTLPD? Blood. 2009; 113:6263–6264. [PubMed: 19520823]

59. Zhang MM, Gopal AK. Radioimmunotherapy-based conditioning regimens for stem cell transplantation. Semin.Hematol. 2008; 45:118–125. [PubMed: 18381107]

60. Press OW, Eary JF, Appelbaum FR, et al. Radiolabeled-antibody therapy of B-cell lymphoma with autologous bone marrow support. N.Engl.J.Med. 1993; 329:1219–1224. [PubMed: 7692295]

61. Gopal AK, Gooley TA, Maloney DG, et al. High-dose radioimmunotherapy versus conventional high-dose therapy and autologous hematopoietic stem cell transplantation for relapsed follicular non-Hodgkin lymphoma: a multivariable cohort analysis. Blood. 2003; 102:2351–2357. [PubMed: 12750161]

62. Winter JN, Inwards D, Spies S, et al. 90Y Ibritumomab Tiuxetan (Zevalin(R); 90YZ) Doses Calculated To Deliver up to 1500 cGy to Critical Organs May Be Safely Combined with High-Dose BEAM and Autotransplant in NHL. ASH Annual Meeting Abstracts. 2006; 108:330.

63. Vose J, Bierman P, Bociek G, et al. Radioimmunotherapy with 131-I tositumomab enhanced survival in good prognosis relapsed and high-risk diffuse large B-cell lymphoma (DLBCL) patients receiving high-dose chemotherapy and autologous stem cell transplantation. ASCO Meeting Abstracts. 2007; 25:8013.

64. 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]

65. 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.

Table 1

Autologous stem cell transplantation outcome in transformed lymphoma.

Ref	Year*	No of patients	Median age (yr)	No of regimens Median (range)	Conditioning regimen	Pre-SCT disease status (CR+PR %)	DFS/ PFS (%)	OS (%)
[40]	2010	12	47	2 (1-4)	BuCy, CyTBI	91	33 (5 year)	58 (5 year)
[39]	2009	25	57	2 (1-11)	CBV	92	59 (3 year)	64 (3 year)
[42]	2008	24	56	2 (1-6)	BuCy, BEAM, CBV	75	33 (5 year)	52 (5 year)
[38]	2007	23	49.6	2	CBV, BEAM	n/a	25 (5 year)	56 (5 year)
[44]	2001	50	40	1 (0-3)	CyTBI±VP16, BEAM or CBV	CR=38	30 (5 year)	51 (5 year)
[37]	2001	35	48	1 (0-4)	VP16MelTBI	100	36 (5 year)	37 (5 year)
[18]	1999	27	44	3 (2-10)	CyTBI	CR=44	46 (5 year)	58 (5 year)
[43]	1998	27	42	3 (1-10)	CyTBI	100	n/a	n/a
[45]	1989	10	42	n/a	CyTBI, CyVP16B, CyAra-CTBI	80	n/a	n/a

Ref, reference number;

*, year of publication;

No, number; yr, year; SCT, stem cell transpla ntation; CR, complete remission; PR, partial remission; DFS, disease free survival; OS, overall survival; Cy, cyclophosphamide; VP16, etoposide; TBI, total body irradiation; BEAM, carmustine, etoposide, cytarabine, and melphalan; CBV, cyclophosphamide, carmustine, etoposide; BuCy, busulfan, cyclophosphamide; Mel, melphalan; Ara-C, cytarabine; PFS, progression free survival.

Table 2

Allogeneic stem cell transplantation outcome in transformed lymphoma

Ref	Year*	No of patients	Median age (yr)	No of regimens Median (range)	Conditioning regimen	Pre-SCT disease status (CR+PR %)	DFS/ PFS (%)	OS (%)
[51]	2010	19	57	2 (1-4)	FluBu	100	68 (4 year)	68 (4 year)
[53]	2009	5	47	4 (3-6)	BuCy	80	80 (5 year)	100 (5 year)
[54]	2008	25	44	3(1-4)	Cy/TBI VP-16+Cy/TBI	60	25 (3 year)	48 (3 year)
[52]	2008	18	46	5 (2-7)	Campath, Flu, Mel (RIC)	83	55 (4 year)	54 (4 year)
[50]	2008	16	54	6 (1-19)	FluTBI200	63	18 (3 year)	21 (3 year)
[55]	2008	8	57	N/A	BuCy, FluBuATG	62	56 (4 year)	66 (4 year)
[49]	2005	16	40	2	CyVP16TBI	87	38 (5 year)	

Ref, reference number;

*, year of publication;

No, number; yr, year; SCT, stem cell transplantation; CR, complete remission; PR, partial remission; DFS, disease free surviva l; OS, overall survival; Flu, fludarabine; Mel, melphalan; RIC, reduced intensity conditioning regimen; TBI, total bod y irr adi ation; 200, 200 cGY; VP16, etoposide; Cy, cyclophosphamide; Bu, busulfan; PFS, progression free survival; EFS, event free survival.