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Transformation in Follicular lymphoma: Biology, prognosis, and therapeutic options

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Abstract
The transformation of follicular lymphoma into an aggressive histology is a well-recognised complication that occurs at a rate of approximately 3% a year for the first 10 years of observation. Transformation is accompanied by increased risk of refractoriness to treatment and a poor expectation of survival. Genetic and epigenetic triggers for transformation have been described. Where transformed lymphoma has been managed in a similar fashion to de-novo diffuse large-cell lymphoma the outcomes have generally been poor. Rituximab appears to have improved outcomes. Some centres including our own use high-dose chemotherapy with stem cell transplantation as consolidation for those with responsive disease. Here, we focus on transformed follicular lymphoma, provide an overview of the current literature and our approach to management.

Introduction

The natural history of indolent non-Hodgkin B-cell lymphomas is of a chronic course with repeated relapses following responses to systemic therapies or radiotherapy[1]. Histological transformation of indolent B-cell lymphomas to an aggressive lymphoma occurs in a subset of patients. Transformation of follicular lymphoma (FL) into diffuse large B-cell lymphoma (DLBCL) is the most frequently encountered and best described example of transformation, and will be the focus of this review. Many of the clinical series include marginal zone lymphomas, and there is a separate literature describing the management of transformed chronic lymphocytic leukaemia. Importantly, the majority of natural history studies of FL and descriptions of transformation precede the inclusion of rituximab in routine therapy. The natural history of transformation may now be different. The prognosis of transformed FL is, with the exception of patients presenting with limited stage disease, poor, and in our view the limited available evidence supports treatment with high dose therapy and stem cell transplantation, where possible. This review focuses on the current knowledge of the incidence, risk factors and prognosis of patients with transformed FL, and presents the evidence for available therapeutic options with an emphasis on recently published data.

Incidence of and Definition of Transformed Follicular Lymphoma

There is a lack of a uniform definition of transformed follicular lymphoma. It is universally accepted that histological change from FL to DLBCL or Burkitt/Burkitt-like morphology represents disease transformation. A more difficult distinction is where there is progression from grade 1 or 2 FL to grade 3a disease. On the other hand, most accept that grade 3b FL with sheets of large centroblasts represents DLBCL and would include anthracycline in chemotherapy. While histological evidence of transformation remains the gold standard, histological sampling may in certain circumstances be impractical. A clinical diagnosis of transformation may be made in patients with prior known low-grade disease based on a combination of clinical features including rapid or discordant tumour growth and new B symptoms, or a rapid rise in serum lactate dehydrogenase (LDH).

The incidence of transformation from FL to a more diffuse and aggressive phenotype ranges from 20-30% over 10 years of follow up in retrospective analyses[2-5]. Autopsy series report rates of transformation up to 70%, suggesting that it is a common terminal event in patients with FL[6]. The largest retrospective analysis of the incidence of transformed FL was reported by Al-Tourah et al[2]. Diagnosis of transformation was made on histological transformation to DLBCL or Burkitt-like lymphoma or on clinical criteria of a sudden rise in LDH to at least 2 times the upper limit of normal, rapid discordant localised nodal growth detected clinically or radiologically, new involvement of unusual extra-nodal sites, new B symptoms or development of new hypercalcemia. Over a median follow-up of 111 months, 28% were diagnosed with transformation, with a 10 year risk of 30% without evidence of a risk-plateau at 15 years[2]. Bastion et al[3] included in their

series patients with transformed disease diagnosed either clinically (rapidly growing bulky disease, B symptoms, high LDH) or histologically and found a probability of transformation of 31% at 10 years. In two recent reports, Montoto et al[5] and Conconi et al[4] described rates of histological transformation at 10 years of 28% and 15% respectively. Both of these reports identified a plateau in transformation risk at 14 to 16 years after initial diagnosis, although only 6 patients remained at risk beyond 20 years in the Conconi study.

Positron Emission Tomography (PET) Scanning For Diagnosis of Transformation

^{18}Fluorodeoxyglucose positron emission tomography (PET) is more sensitive than conventional anatomical staging modalities, and can discriminate between high and low-grade disease. Initial observations that aggressive lymphomas have tendency towards a higher standardised uptake variable (SUV) than low-grade lymphoma[7] have been confirmed in transformed disease. [8, 9] In a retrospective series of 28 patients with indolent lymphoma and clinical suspicion of transformation, a maximal SUV of 14 or greater had a specificity of 93.9% and sensitivity of 95.3% for transformed disease. [8] PET is therefore a useful tool to raise suspicion of transformation and can be used to choose the best location to biopsy to prove transformed disease.

Risk Factors for Transformation

Clinicopathological risk factors

Several risk factors for transformation of FL have been identified. Unsurprisingly patients who present with advanced stage FL are at a higher risk of transformation[2, 5]. Other risk factors include involvement of extranodal sites other than bone marrow[4], grade 3 histology[10], higher Follicular Lymphoma International Prognostic Index (FLIPI) score[10, 5], and non-achievement of complete remission after initial therapy[3]. Variables which have not consistently been associated with an increased risk of transformation include serum beta-2-microglobulin and LDH, Eastern Cooperative Oncology Group (ECOG) performance status, and the presence of bone marrow involvement with lymphoma[4, 3].

Influence of previous treatment

The influence of timing and choice of initial treatment on transformation risk is uncertain. In patients with initially asymptomatic FL, long-term survival following an initial period of observation in selected patients is equivalent those receiving immediate therapy. [11] Analysis of a cohort of patients with indolent NHL by Horning and Rosenberg[1] showed that there was no difference in the incidence of histologic transformation and the time to transformation in patients who were managed expectantly compared with those who received immediate cytotoxic therapy with radiotherapy, chemotherapy, or combined chemoradiation. This has been confirmed in a larger and more recent retrospective analysis. [4] However, in the cohort of FL patients comprising the National Lymphocare Study (NLCS), patients with stage III or IV FL were reported as having a higher risk of transformation if managed with watchful waiting compared to chemoimmunotherapy.[12] For patients who require initial management with cytotoxic therapy, the effect of chemotherapy regimen on future risk of transformation is unclear. Anthracycline-containing regimens may reduce the risk of transformation compared to alkylator-purine analogue combinations. The study by Al-Tourah et al [2] reported a transformation rate of 18 and 30% at ten years for each group respectively. To our knowledge, there are no prospective data to allow firm conclusions. [2, 13]

Biology of Transformation

Genetic mutation, epigenetic mechanisms and alterations to the tumour microenvironoment have been implicated in the pathogenesis of transformation. However, no single, unifying recurrent mechanism has been identified.

Follicular lymphoma cells are unique amongst other types of non-hodgkin lymphoma in that the process of somatic hypermutation persists. Follicular lymphoma cells from a single biopsy are heterogenous with respect to immunoglobulin (Ig) VDJ rearrangements.[14] Within a single tumour, clones, each with varying potential for transformation exist. Rossi et al[15] examined the frequency of aberrant somatic hypermutation in a panel of genes including the proto-oncogenes PIM-1, PAX-5 and c-MYC in cases of transformed FL, and identified that these genes had undergone mutational change at the time of transformation to DLBCL, mostly resulting from single nucleotide substitutions. Analyses of biopsy samples obtained from patients at initial diagnosis of FL and subsequently at transformation have identified mutations of several different proto-oncogenes including TP53, CDK2A and c-REL. These observations have been identified in additional cohorts.[16-18] Mutations have also been identified in coding and non-coding sequences of bcl-6, which encodes a POZ-Zinc finger protein that functions as a DNA-binding transcription repressor[15, 19]. None of these mutations have been consistently identified in all cases of transformed FL, indicating that transformation of FL can occur by several different oncogenic pathways.

Transformation of FL was previously thought to arise from evolution of a single FL clone. Two series have independently identified the presence of a common progenitor cell (CPC) from which both FL and transformed FL may arise[20, 21]. Analysis of immunoglobulin gene sequences from biopsies taken at diagnosis and at subsequent transformation have allowed the construction of geneologic trees which support the contention that in some cases an undifferentiated B-cell population is present throughout the course of disease, and gives rise to both the initial indolent FL as well as transformed disease. Alternatively, in some cases a new clone arises later in the course of the disease, closer o the time of clinical transformation.

Role of the tumour microenvironment

The tumour microenvironment may affect tumor cell survival and prognosis. A particular role appears to exist for neighbouring T cells, with an association observed between a greater number of CD4+ T cells in the intrafollicular compartment and an increased likelihood of transformation to DLBCL[22]. Intrafollicular CD4+ T cells in biopsies of transformed FL are also more likely to be in an activated state as indicated by higher CD69 expression[23]. It uncertain whether this is a bystander effect or a causative factor, however it is possible that the cellular milieu contributes to transformation. Glas et al[23] observed that pro-inflammatory genes were more likely to be expressed in transformed FL compared to non-transformed disease. Additionally, a decreased number of tumour-infiltrating FOXP3-positive regulatory T cells correlates with poorer survival in patients with FL as well as a greater likelihood of transformation to DLBCL[24].

Potential biomarkers of transformation risk

Genome-wide association studies (GWAS) have identified single nucleotide polymorphisms (SNP) that are associated with an increased susceptibility to development of FL and subsequent transformation[25, 26]. Wrench et al[27] reported that variant alleles in the human leukocyte antigen (HLA) region on chromosome 6p21 are associated with a higher incidence of transformation of FL as well as a shorter time to transformation. However, the precise coding locus that is involved in the transformation process is unclear.

Prognosis

The prognosis of patients with transformed FL is poor. While FL typically follows an indolent course and has a median survival from diagnosis of 7 to 10 years, the median duration of survival following disease transformation in patients treated with conventional chemotherapy regimens including CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) or other similar anthracycline-containing regimens ranges from 7 to 20 months[2, 3, 10, 5]. In the series by Bastion

et al[3] which included 52 patients with transformed FL, patients who either did not receive an anthracycline or did not receive treatment had a median survival of 4 months from transformation. Survival data from the rituximab era are limited but rituximab does appear to improve outcomes in the rituximab naive. [28] Factors that are associated with longer survival following transformation include stage I or II disease (accounting for only the minority of cases), the absence of B symptoms and bone marrow involvement, normal LDH, age less than 60 years, and an Eastern Cooperative Oncology Group (ECOG) performance status less than 1[3]. The poor prognosis for patients with transformed FL underscores the need for more effective therapy than conventional combination regimens typically given to large B cell lymphomas such as R-CHOP.

Treatment of transformed follicular lymphoma

Standard Chemotherapy

The outcomes of patients with transformed FL managed with DLBCL-type regimens including CHOP have generally been poor. There is however a subset of patients who may achieve a good response with these regimens. In the transformed FL study from British Colombia[2] patients with limited disease at the time of transformation (single nodal region, limited extranodal involvement, non-bulky disease, no B-symptoms) received 3 cycles of CHOP with involved field radiotherapy. Overall survival at 5 years was 66%, indicating that this select group of patients with favourable risk factors can be managed with this regimen alone. The addition of rituximab to CHOP appears on the basis of a retrospective review to substantially improve overall survival in this patient group, consistent with phase III trial data in follicular lymphoma and diffuse large B-cell lymphoma[28]. As a consequence, R-CHOP is the standard of care in most centres , particularly patients who are treatment naive or who have limited prior anthracycline exposure. It is our experience, however, that majority of patients with transformed FL warrant alternative therapy, due to prior exposure to anthracycline. These patients should receive treatment with salvage regimens such as ifosfamide, carboplatin, etoposide (ICE) combined with rituximab. Where feasible, we usually consolidate a response with high dose chemotherapy and autologous stem cell support.

Radioimmunotherapy

Studies published in the 1990's described the efficacy of radioimmunoconjugates in B-cell lymphomas[29, 30]. More recently, Witzig et al[31] reported a response rate of 56% in patients with transformed CD20 positive NHL after 4 weeks of Y-90 ibritumomab. Kaminski et al[32] evaluated the efficacy of I-131 tositumomab in patients with chemotherapy refractory low-grade or transformed low-grade NHL in a multicentre non-randomised study. Of the 23 patients with transformed lymphoma, the overall response rate was 39%; 13% achieved a CR. The median duration of response was 6.5 months.

The largest single analysis of the efficacy of radioimmunotherapy with I-131 tositumomab in patients with relapsed, refractory and transformed low-grade NHL was reported by Fisher et al[33]. This was a pooled analysis of 5 clinical trials with a combined total of 250 patients, of which 28% of patients had transformed disease. The overall response rate was 56%, with 30% of patients achieving CR. The median duration of response was 12.9 months.

The place of radioimmunotherapy in the overall schema of treatment of transformed FL is unclear. Its limited role in aggressive lymphomas argues against its use front line It may prove to have a role as an adjunct to ASCT, and has been proven to have a favourable toxicity profile.

High-dose chemotherapy and autologous stem cell transplantation (ASCT) as consolidation for salvage treatment

Although there are limited data on the role of ASCT in this setting, collectively it suggests an improved outcome over standard regimens. [3, 2]. The majority of data supporting the efficacy of ASCT in transformed FL comes from retrospective analyses (table 1)[34-39]. These studies are

generally limited to subjects with a known history of low grade lymphoma, have included relatively small sample sizes (*N*=22-50) with median durations of follow-up between 4-8 years following transplantation. They suggest that treatment with ASCT results in an overall survival (OS) of between 37-56% at 5 years, and PFS of between 25-35% at 5 years. Median OS after transplantation ranged between 33-55 months. The largest retrospective analysis of high-dose chemotherapy with ASCT in transformed FL was that from the European Bone Marrow Transplant Lymphoma Registry[39]. Fifty patients were included in this analysis. All patients had received at least 1 prior line of therapy prior to ASCT, and the majority of patients had chemosensitive disease. High-dose regimens used included total-body irradiation, and BEAM (BCNU, etoposide, cytarabine, melphalan). Following ASCT, 62% of patients attained CR at 100 days, with 14.6% achieving PR. The OS at 5 years was 51%, with PFS 30%. Relapse, however, was common. After a median follow-up period of 4years 11months, 50% of patients developed disease relapse.

The only prospective study of high dose therapy and ASCT in transformed indolent B-cell lymphomas was a multicentre Norwegian study[36]. Forty-six of the 47 patients had transformed FL. Patients were required to have chemosensitive disease to be eligible for ASCT. High dose therapy consisted of the standard BCNU, etoposide, cytarabine and melphalan protocol (BEAM). Complete remission was achieved in 60% of patients after ASCT, and 23% of patients achieved PR after 3 months. Seventeen percent of patients had non-responsive disease. Overall survival after 5 years was 47% and median overall survival time was 47 months, results comparable the previously described retrospective data.

Identification of pre-transplant predictors of improved response will allow a more robust selection of patients who are more likely to benefit from ASCT. Chemosensitive disease prior to high dose therapy is predictive of superior post-transplant outcomes[38, 39], and as for denovo DLBCL, chemoresistant transformed disease may be viewed as a contraindication to ASCT. The depth of response to salvage therapy appears to not affect post-transplant outcome. Patients who achieve either PR or CR after salvage chemotherapy but prior to transplantation having similar rates of OS and PFS[34, 35]. Age less than 60 years is predictive of superior outcomes following ASCT[35, 34].

There is a paucity of data regarding the efficacy of ASCT compared to rituximab-containing standard-dose chemotherapy, as well as the utility of ASCT to consolidate a response obtained with chemotherapy-rituximab salvage. In an unpublished retrospective series from the Canadian Blood and Marrow Transplant Group (CBMTG)[40]. The authors reported that while 5-year PFS was superior in patients who received ASCT compared to rituximab-based chemotherapy, there was no difference in OS after 5 years.

A small retrospective series by Ban-Hoefen et al[41] suggests an ongoing role for ASCT in the rituximab era. With a median follow up of 3 years, the authors reported a 2 year OS and PFS were 82% and 59% respectively. These results compare favourably to survival data published for patients in the pre-rituimab era, with 2 year OS ranging from 60-70%[35, 42, 38, 39]. Larger series with longer follow up are needed.

Finally, there may be a role for autologous stem cell transplantion in patients who are found to have elements of both low and high grade lymphoma at diagnosis, or so-called discordant lymphoma. Ghesquieres et al[43] described 60 patients with DLBCL who concurrently had coexisting of low-grade lymphoma. Twenty-two patients had follicular lymphoma; the remainder had marginal zone lymphoma or CLL. These patients had a similar 5-year survival compared to a matched group with pure denovo DLBCL (57 vs 62%; p=0.21) but a substantially poorer freedom from progression (33 vs 57% respectively, p=0.03). A univariate analysis comparing the survival of 37 patients treated with sequential chemotherapy to the 23 consolidated with up-front ASCT at first CR or PR

suggested an improved overall survival in the latter group (figure 1). No definitive recommendation can be drawn from this study with a heterogenous mix underlying low-grade lymphoma however it may suggest a role or ASCT as an upfront approach in this group.

Allogeneic Stem Cell Transplantation

Compared with ASCT, allogeneic stem cell transplantation (allo-SCT) has the theoretical benefits of providing a tumour-free graft and maintaining anti-lymphoma activity beyond the conditioning regimen through a graft-versus-lymphoma effect, potentially reducing the rate of relapse. Study cohorts for allo-SCT in transformed FL have been small. The largest published series is that of patients with transformed lymphoma who underwent allo-SCT in British Columbia up to 2005[42]. Patients in this cohort received myeloablative conditioning. The median overall survival from the time of allo-SCT was 11 months; 5 year OS was 23%. The rate of disease relapse was high, with 35% of patients developing relapsed disease at a median of 128 days following allo-SCT. Treatment-related mortality was a significant 38%. These results are mirrored in a cohort reported by Doocey et al[44], which included 16 patients with transformed lymphoma who received allo-SCT with myeloablative conditioning. Overall survival at 5 years was 38%, and treatment related mortality was 50%. In a recent unpublished series comparing autologous with allogeneic SCT, overall survival and progression-free survival were similar, however transplant related mortality was significantly higher in patients who underwent allo-SCT[45]. Causes of non-relapse mortality with allo-SCT include acute graft-versus-host disease (GVHD), infection, veno-occlusive disease, and atherosclerotic heart disease. Age at transplantation, together with number of prior therapies are a significant factors contributing to TRM and are especially relevant to consider when interpreting the published data. [42].

In order to reduce treatment related mortality, reduced-intensity conditioning (RIC) with non-myeloablative regimens have been used. However, TRM remains significant and overall response is poor in transformed lymphoma. Rezvani et al[46] reported outcomes after non-myeloablative allo-HCT in patients with refractory, relapsed or transformed indolent non-Hodgkin's lymphoma. While the majority of patients achieved a response, this was tempered by non-relapse mortality (NRM) of 42% after 3 years. Overall survival for the cohort was 18% at 3 years, and patients with transformed disease had an even poorer outcome.

One subset of patients who may respond well to RIC allo-SCT are those with evidence of chemosensitive disease prior to allo-SCT. Clavert et al[47] reported a cohort of 19 patients with relapsed or transformed non-Hodgkin's lymphoma proceeded to allo-SCT after achieving CR or PR with initial chemotherapy. Overall survival and PFS were both significantly higher than in previously published cohorts; 4 year OS and PFS were both 66%. This observation that patients with chemosensitive disease have superior outcomes following allo-SCT is not at all unexpected. Doocey et al[44] also noted this on multivariate analysis in their cohort of patients with aggressive NHL. Likewise, Hamadani et al[48] reported that patients with progressive disease prior to allo-SCT had particularly poor outcomes; OS and PFS at 5 years were 21% and 7% respectively. Toxicity with the myeloablative regimen was also significant, with a non-relapse mortality at 100 days of 43% in this group of patients. In patients with stable disease following salvage chemotherapy for relapsed aggressive NHL, the authors reported an acceptable 5 year OS of 46% following alloSCT, with a non-relapse mortality of 9%.

In summary, allogeneic transplantation cannot be recommended in patients with chemo-refractory disease. We reserve allotransplantation for selected younger patients with well matched donors and

high risk but chemosensitive disease. PET response assessments may help stratify risk by establishing whether the aggressive lymphoma has been eradicated prior to transplant.

A management algorithm for transformed follicular lymphoma

The limited quality of published evidence limits the grade of recommendation that can be provided for treatment of transformed lymphoma, however we approach treatment as follows (Table 2). We treat patients with limited disease (single nodal region involved, no B symptoms, non-bulky disease, limited extranodal involvement) and limited treatment history at transformation with chemoimmunotherapy followed by radiotherapy. Where possible we deliver 6 cycles of R-CHOP. In practice we find only the minority of patients who have transformed disease present with early stage disease.

Patients who have evidence of transformation on initial presentation are treated with R-CHOP (or similar) chemotherapy. This is the standard of care in many centres for de-novo transformed lymphoma. However, from the available data in the pre-rituximab era detailing a poor outcome with CHOP alone, we would consider consolidating a response with autologous transplantation in eligible cases after careful discussion with the patient and accepting the limitations of the available data. A small series suggests that the addition of rituximab to CHOP may have improved PFS and OS to results that approach those of CHOP followed by ASCT. [28] For those with prior known follicular lymphoma who relapse with transformed disease, we limit R-CHOP to anthracyline-naïve patients, and generally to those whose last remission was at least 6 months. [43]. We integrate radiotherapy peri-ASCT where feasible and particularly for patients with early stage or dominant bulky sites of disease. At our centre, radioimmunotherpapy is not routinely used for patients with any form of aggressive lymphoma outside the context of a trial.

Referral for allogeneic stem cell transplantation is reserved for younger patients with chemosensitive disease and an available donor.

Future Directions and Conclusion

The safety of maintenance rituximab following ASCT has been demonstrated, [49] and although it is not yet in routine practice, there is a strong rationale for its use in patients with previously transformed disease who are in a CR or who only have low grade disease assessed by PET. It is unlikely that a prospective trial will be performed for patients with transformed disease. Increased research into the biology of paired baseline and “at transformation” samples may identify targets for biological therapies however the heterogeneity of transformed lymphoma suggests that only novel treatments broadly applicable to DLBCL, such as lenalidomide, [50, 51] will prove to be useful in the future. Until then R-CHOP remains the standard of care at most institutions, but there remains a rationale to approach transformed lymphoma as a poor prognosis disease and to consider high dose consolidative treatments when feasible.

Disclosure

No potential conflicts of interest relevant to this article were reported.

References

1. Horning SJ, Rosenberg SA. The natural history of initially untreated low-grade non-Hodgkin's lymphomas. N Engl J Med. 1984;311(23):1471-5.
2. Al-Tourah AJ, Gill KK, Chhanabhai M, Hoskins PJ, Klasa RJ, Savage KJ et al. Population-based analysis of incidence and outcome of transformed non-Hodgkin's lymphoma. J Clin Oncol. 2008;26(32):5165-9.
3. Bastion Y, Sebban C, Berger F, Felman P, Salles G, Dumontet C et al. Incidence, predictive factors, and outcome of lymphoma transformation in follicular lymphoma patients. J Clin Oncol. 1997;15(4):1587-94.
4. Conconi A, Ponzio C, Lobetti-Bodoni C, Motta M, Rancoita PMV, Stathis A et al. Incidence, risk factors and outcome of histological transformation in follicular lymphoma. Br J Haematol. 2012:188-96.
5. Montoto S, Davies AJ, Matthews J, Calaminici M, Norton AJ, Amess J et al. Risk and clinical implications of transformation of follicular lymphoma to diffuse large B-cell lymphoma. J Clin Oncol. 2007;25(17):2426-33.
6. Garvin AJ, Simon RM, Osborne CK, Merrill J, Young RC, Berard CW. An autopsy study of histologic progression in non-Hodgkin's lymphomas. 192 cases from the National Cancer Institute. Cancer. 1983;52(3):393-8.
7. Schöder H, Noy A, Gönen M, Weng L, Green D, Erdi YE et al. Intensity of 18Fluorodeoxyglucose Uptake in Positron Emission Tomography Distinguishes Between Indolent and Aggressive Non-Hodgkin's Lymphoma. J Clin Oncol. 2005;23(21):4643-51.
8. Bodet-Milin C, Kraeber-Bodéré F, Moreau P, Campion L, Dupas B, Le Gouill S. Investigation of FDG-PET/CT imaging to guide biopsies in the detection of histological transformation of indolent lymphoma. Haematologica. 2008;93(3):471-2.
9. •Noy A, Schöder H, Gönen M, Weissler M, Ertelt K, Cohler C 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(3):508-12. *Described the utility of standardised uptake values in identifying transformed lymphoma.*
10. Giné E, Montoto S, Bosch F, Arenillas L, Mercadal S, Villamor N 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(10):1539-45.
11. Ardeshna KM, Smith P, Norton A, Hancock BW, Hoskin PJ, MacLennan KA et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet. 2003;362(9383):516-22.
12. Sinha R, Byrtek M, De Joubner N, Nooka A, Taylor M, Cerhan J et al. Examining the Outcomes of Watchful Waiting Among US Patients with Advanced Stage Follicular Lymphoma [abstract 775]. American Society of Haematology Conference2011.
13. Cohen Y, Da'as N, Libster D, Amir G, Berrebi A, Polliack A. Large-cell transformation of chronic lymphocytic leukemia and follicular lymphoma during or soon after treatment with fludarabine-rituximab-containing regimens: natural history- or therapy-related complication? Eur J Haematol. 2002;68(2):80-3.
14. Matolcsy A, Schattner EJ, Knowles DM, Casali P. Clonal evolution of B cells in transformation from low- to high-grade lymphoma. Eur J Immunol. 1999;29(4):1253-64.
15. Rossi D, Berra E, Cerri M, Deambrogi C, Barbieri C, Franceschetti S et al. Aberrant somatic hypermutation in transformation of follicular lymphoma and chronic lymphocytic leukemia to diffuse large B-cell lymphoma. Haematologica. 2006;91(10):1405-9.

16. Davies AJ, Rosenwald A, Wright G, Lee A, Last KW, Weisenburger DD et al. Transformation of follicular lymphoma to diffuse large B-cell lymphoma proceeds by distinct oncogenic mechanisms. Br J Haematol. 2007;136(2):286-93.
17. Gentles AJ, Alizadeh AA, Lee S-I, Myklebust JH, Shachaf CM, Shahbaba B et al. A pluripotency signature predicts histologic transformation and influences survival in follicular lymphoma patients. Blood. 2009;114(15):3158-66.
18. Symmans WF, Katz RL, Ordoñez NG, Dalton H, Romaguera JE, Cabanillas F. Transformation of follicular lymphoma. Expression of p53 and bcl-2 oncoprotein, apoptosis and cell proliferation. Acta Cytol. 1995;39(4):673-82.
19. Szereday Z, Csernus B, Nagy M, László T, Warnke RA, Matolcsy A. Somatic mutation of the 5' noncoding region of the BCL-6 gene is associated with intraclonal diversity and clonal selection in histological transformation of follicular lymphoma. Am J Pathol. 2000;156(3):1017-24.
20. Carlotti E, Wrench D, Matthews J, Iqbal S, Davies A, Norton A 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(15):3553-7.
21. Eide MB, Liestøl K, Lingjaerde OC, Hystad ME, Kresse SH, Meza-Zepeda L et al. Genomic alterations reveal potential for higher grade transformation in follicular lymphoma and confirm parallel evolution of tumor cell clones. Blood. 2010;116(9):1489-97.
22. Martinez A, Carreras J, Campo E. The follicular lymphoma microenvironment: From tumor cell to host immunity. Current Hematologic Malignancy Reports. 2008;3(4):179-86.
23. Glas AM, Knoops L, Delahaye L, Kersten MJ, Kibbelaar RE, Wessels LA 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(4):390-8.
24. Carreras J, Lopez-Guillermo A, Fox BC, Colomo L, Martinez A, Roncador G et al. High numbers of tumor-infiltrating FOXP3-positive regulatory T cells are associated with improved overall survival in follicular lymphoma. Blood. 2006;108(9):2957-64.
25. Skibola CF, Bracci PM, Halperin E, Conde L, Craig DW, Agana L et al. Genetic variants at 6p21.33 are associated with susceptibility to follicular lymphoma. Nat Genet. 2009;41(8):873-5.
26. Akers NK, Curry JD, Conde L, Bracci PM, Smith MT, Skibola CF. Association of HLA-DQB1 alleles with risk of follicular lymphoma. Leuk Lymphoma. 2011;52(1):53-8.
27. Wrench D, Leighton P, Skibola CF, Conde L, Cazier J-B, Matthews J et al. SNP rs6457327 in the HLA region on chromosome 6p is predictive of the transformation of follicular lymphoma. Blood. 2011;117(11):3147-50.
28. Al-Tourah AJ, Savage KJ, Gill KK, Klasa RJ, Sehn LH, Shenkier TN et al. Addition of Rituximab to CHOP Chemotherapy Significantly Improves Survival of Patients with Transformed Lymphoma. ASH Annual Meeting Abstracts. 2007;110(11):790-.
29. Witzig TE, White CA, Wiseman GA, Gordon LI, Emmanouilides C, Raubitschek A et al. Phase I/II Trial of IDEC-Y2B8 Radioimmunotherapy for Treatment of Relapsed or Refractory CD20+ B-Cell Non-Hodgkin's Lymphoma. J Clin Oncol. 1999;17(12):3793-803.
30. Kaminski MS, Zasadny KR, Francis IR, Fenner MC, Ross CW, Milik AW et al. Iodine-131-anti-B1 radioimmunotherapy for B-cell lymphoma. J Clin Oncol. 1996;14(7):1974-81.
31. Witzig TE, Gordon LI, Cabanillas F, Czuczman MS, Emmanouilides C, Joyce R et al. Randomized Controlled Trial of Yttrium-90–Labeled Ibritumomab Tiuxetan Radioimmunotherapy Versus Rituximab Immunotherapy for Patients With Relapsed or Refractory Low-Grade, Follicular, or Transformed B-Cell Non-Hodgkin’s Lymphoma. J Clin Oncol. 2002;20(10):2453-63.
32. Kaminski MS, Zelenetz AD, Press OW, Saleh M, Leonard J, Fehrenbacher L 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(19):3918-28.
33. Fisher RI, Kaminski MS, Wahl RL, Knox SJ, Zelenetz AD, Vose JM 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(30):7565-73.
34. Andreadis C, Schuster SJ, Chong EA, Svoboda J, Luger SM, Porter DL 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(11):955-61.
35. Chen CI, Crump M, Tsang R, Stewart AK, Keating A. Autotransplants for histologically transformed follicular non-Hodgkin's lymphoma. Br J Haematol. 2001;113(1):202-8.
36. ••Eide MB, Lauritzsen GF, Kvalheim G, Kolstad A, Fagerli UM, Maisenhölder M 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(5):600-10.
The only prospective study of high dose chemotherapy with autologous stem cell transplantation in transformed lymphoma.
37. Hamadani M, Benson DM, Lin TS, Porcu P, Blum KA, Devine SM. High-dose therapy and autologous stem cell transplantation for follicular lymphoma undergoing transformation to diffuse large B-cell lymphoma. Eur J Haematol. 2008;81(6):425-31.
38. Sabloff M, Atkins HL, Bence-Bruckler I, Bredeson C, Fergusson D, Genest P 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(8):956-64.
39. Williams CD, Harrison CN, Lister TA, Norton AJ, Blystad AK, Coiffier B 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(3):727-35.
40. D. Villa KS, M. Crump, C. Toze, M. Rubinger, C. Lee, M. Alzahrani, R. Foley. "Focus on…" session: high-dose chemotherapy. Ann Oncol. 2011;22(suppl 4):iv115-iv6.
41. •Ban-Hoefen M, Kelly JL, Bernstein SH, Liesveld J, Constine L, Becker M et al. High-dose therapy and autologous stem cell transplant for transformed non-Hodgkin lymphoma in the rituximab era. Leuk Lymphoma. 2012;53(5):830-5.
A retrospective analysis of ASCT in transformed lymphoma in patients previously exposed to rituximab.
42. Ramadan KM, Connors JM, Al-Tourah AJ, Song KW, Gascoyne RD, Barnett MJ et al. Allogeneic SCT for relapsed composite and transformed lymphoma using related and unrelated donors: long-term results. Bone Marrow Transplant. 2008;42(9):601-8.
43. Ghesquières H, Berger F, Felman P, Callet-Bauchu E, Bryon P-A, Traverse-Glehen A 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(33):5234-41.
44. Doocey RT, Toze CL, Connors JM, Nevill TJ, Gascoyne RD, Barnett MJ et al. Allogeneic haematopoietic stem-cell transplantation for relapsed and refractory aggressive histology non-Hodgkin lymphoma*. Br J Haematol. 2005;131(2):223-30.
45. Villa. Lugano ASCT transformed lymphoma. Ann Oncol. 2011;22(Supplement 4):iv10-iv24.
46. Rezvani AR, Storer B, Maris M, Sorror ML, Agura E, Maziarz RT et al. Nonmyeloablative Allogeneic Hematopoietic Cell Transplantation in Relapsed, Refractory, and Transformed Indolent Non-Hodgkin's Lymphoma. J Clin Oncol. 2008;26(2):211-7.
47. Clavert A, Le Gouill S, Brissot E, Dubruille V, Mahe B, Gastinne T et al. Reduced-intensity conditioning allogeneic stem cell transplant for relapsed or transformed aggressive B-cell non-Hodgkin lymphoma. Leuk Lymphoma. 2010;51(8):1502-8.
48. Hamadani M, Benson DM, Hofmeister CC, Elder P, Blum W, Porcu P et al. Allogeneic Stem Cell Transplantation for Patients with Relapsed Chemorefractory Aggressive Non-Hodgkin Lymphomas. Biol Blood Marrow Transplant. 2009;15(5):547-53.
49. Pettengell R, Schmitz N, Gisselbrecht C, Smith G, Patton WN, Metzner B et al. Rituximab Purging and Maintenance Improves Progression Free Survival but Not Overall Survival In Patients

with Relapsed or Resistant Follicular Lymphoma Prior Receiving An Autologous Transplant. ASH Annual Meeting Abstracts. 2010;116(21):3567-.
50. Czuczman MS, Vose JM, Witzig TE, Zinzani PL, Buckstein R, Polikoff J 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(4):477-81.
51. Witzig TE, Vose JM, Zinzani PL, Reeder CB, Buckstein R, Polikoff JA et al. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B-cell non-Hodgkin's lymphoma. Ann Oncol. 2011;22(7):1622-7.

Figure 1: Overall survival of patients with an initial presentation of transformed lymphoma treated with conventional chemotherapy (ACVBP or CHOP alone , n-37) or with conventional chemotherapy followed by high dose chemotherapy and ASCT (n=23). This series included 22 patients with follicular lymphoma, 32 with marginal zone lymphoma and six with SLL. (With permission from [43].)

Figure 1:

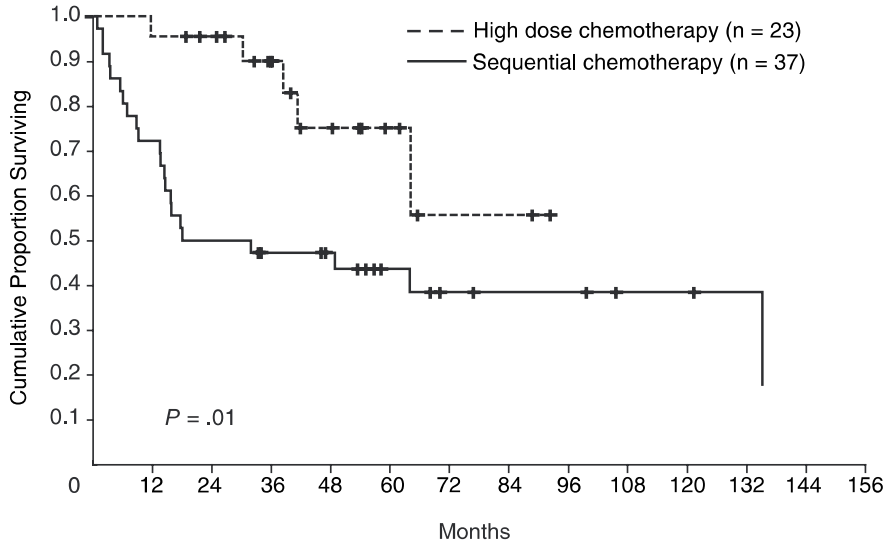
High dose chemotherapy (n = 23)
Sequential chemotherapy (n = 37)
Cumulative Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
P = .01
0
12
24
36
48
60
72
84
96
108
120
132
144
156
Months

Table 1. High-dose chemotherapy with autologous stem cell transplantation (ASCT) for transformed indolent NHL: published series from year 2000

Authors	Year	Indolent NHL subtype	No.	Rituximab in salvage regimen	TBI as part of conditioning	Response to HDT	OS	PFS	Treatment related mortality
Chen et al[35]	2001	FL	35	No	TBI Mel Etop in 92%	Not reported	37% (5yrs) 33months (median)	21 months (median)	20% at 100days 9% MDS
Williams et al[39]	2001	FL	50	No	TBI 70%	62% CR; 14% PR	51% (5yrs)	30% (5yrs) 13months (median)	8% TRM at 100days
Andreadis et al[34]	2005	FL	22	No	51% TBI	50% CR	4.6 years (median)	1.4 years (median)	2% TRM at 100days
Sabloff et al[38]	2007	FL	23	No	No	Not reported	56% (5yrs)	25% (5yrs)	0 TRM at 100days
Hamadani et al[37]	2008	FL	24	62% ritux	No	66% CR; 8% PR	52% (5yrs)	33% (5yrs)	Non-relapse mortality 8% (day 100)
Eide et al[36]	2011	Indolent NHL (FL, MZL)	32	No	No	60% CR; 23% PR	47% (5yrs) 47months (median)	32% (5yrs) 26months (median)	0 TRM at 100days

Stage I/II and may be incorporated into radiation field, no B symptoms, non bulky disease	Rituximab- Chemotherapy* + Radiotherapy Consider stem cell harvest
Late stage, transplant ineligible	Rituximab-Chemotherapy* + CNS prophylaxis if indicated
Late stage, transplant eligible	Rituximab - Chemotherapy* and consideration of consolidation autograft or allograft +/- additional CNS prophylaxis

Table 2: Our approach to the initial presentation of transformed lymphoma. *R-CHOP x6 cycles when the patient presents de-novo with transformed/discordant disease. In patients with previous known lymphoma we reserve R-CHOP for those who are anthracycline naïve and generally where the prior remission is >6 months. Otherwise chemotherapy should be salvage such as ifosfamide/carboplatin/etoposide with rituximab.