The incidence, natural history, biology, and treatment of transformed lymphomas

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Treatment of patients with transformed lymphoma presents a significant challenge to the practicing physician. Indeed, the transformation of follicular lymphoma to a more aggressive histology is inherent to the biology of this disease and is often associated with an aggressive clinical course, resulting in a poor prognosis. Recent population-based studies have better defined the incidence of this event, and recent laboratory studies have defined the molecular and immunological processes associated with transformation. These studies will be discussed in this review, as will the treatment options for these patients.

One of the earliest descriptions of transformation of a low grade non-Hodgkin lymphoma (NHL) to a higher histological grade was made in 1942 by Gall and Mallory, who noted that a subsequent biopsy from a patient initially diagnosed with follicular lymphoma (FL) was found to have a "less differentiated appearance."[1] Indeed, they go on to say that, "It is believed reasonable to expect this degree of dedifferentiation in any group of malignant tumors followed over an extended period of time."[1] In 1978, Drs. Cullen, Lister and colleagues reported the first prospective evaluation of chemotherapy-treated patients with indolent lymphoma who had a repeat lymph node biopsy performed at the time of progression.[2] In their series of 30 unselected patients, 27% had pathological evidence of transformation to a higher grade of lymphoma.[2] In 1983, Dr. Saul Rosenberg's group from Stanford described a cohort of 22 patients initially diagnosed with a favorable histological subtype of NHL who ultimately developed a histological conversion to an unfavorable subtype.[3] Histological conversion was often associated with an aggressive clinical course, the median survival for these patients being less than 1 year from the time of histological conversion.[3] Decades later, the histological conversion, or transformation, of indolent FL continues to be associated with a poor prognosis. This review discusses recent studies defining the incidence, natural history, biology and treatment of transformed lymphomas (TL).

How Do You Define Transformed Lymphoma?

The lack of a uniform definition of TL complicates the interpretation and comparison of the various case series. All agree that grade 1 or 2 FL followed by a diffuse large cell lymphoma (DLCL) or a Burkitt/Burkitt-like lymphoma is TL. In contrast, progression from FL grade 1/2 to FL grade 3 is often not considered TL, whereas progression from FL grade 3 to a frank DLCL is often considered TL. There are other less overt patterns of histologic transformation that may or may not provide an explanation for an abruptly worsening clinical course; examples include a patient with a predominantly follicular pattern at diagnosis whose putative TL demonstrates an overtly diffuse architecture or a predominantly marginal zone pattern. Unusual histologies are also seen at transformation.[4-6] For example, transformation from a FL to a disease morphologically identical to HD and, remarkably, to dendritic cell neoplasms have been reported.[7] Detailed molecular assays showed that these represent bona fide "transformation" events rather than merely composites of a low-grade FL with another lymphoma.

TL usually maintains a phenotype suggestive of germinal center derivation. The most common immunophenotype is the same as that of FL, $CD10^+/BCL6^+$. Changes in antigenic patterns with transformation are common, such as loss of CD10 and even gain of CD5.[8] Therefore, in a patient with a prior diagnosis of FL, almost any B-cell histology, regardless of immunophenotype, is most likely a TL rather than a second unrelated B-cell malignancy. An antigenic change that should prompt concern for a second malignancy, as opposed to TL, is a change in light chain restriction from kappa to lambda or vice versa.

Some of the reported clinical TL series include patients for whom a biopsy was not obtained but who had a clinical picture consistent with TL.[9,10] For example, in the series of Al-Tourah and colleagues, a clinical diagnosis of TL was made when the patient had either a sudden rise in LDH, rapid discordant localized nodal growth, new involvement

of unusual extranodal sites, new "B" symptoms, or new hypercalcemia.[9] Similarly Bastion and colleagues included patients in their series defined clinically, when a biopsy could not be done, by meeting the following criteria: rapidly growing bulky disease, poor performance status and/or "B" symptoms, and a high LDH.[10] Finally, to exclude patients who may have had a discordant histology at diagnosis (that was not seen on the initial biopsy specimen), some series require that the diagnosis of TL be made only if the patient is more than 6 months from initial diagnosis of FL.[10]

In all cases of progression after an initial diagnosis of FL, especially if there is a high clinical suspicion of transformation based on the clinical and laboratory findings described above, a biopsy should be obtained. As transformation can be focal, a positive emission tomography (PET) scan may help determine the optimal site to biopsy. Noy and colleagues examined the standardized uptake value (SUV) of the biopsy site in 33 patients with histologically confirmed TL.[11] The SUV at the biopsy site ranged from 3 to 38 (median of 12), with 55% of the patients having an SUV higher than 10 and 48% higher than 13.[11] As such, the likelihood of obtaining a biopsy of TL is enhanced if the biopsy is directed to the site with the greatest SUV.

What Is the Incidence of TL?

There is wide variation in the reported incidence of TL due to differences in how it is defined, the length of follow-up of the study, whether a biopsy is mandatory for making a diagnosis, or whether it is an autopsy study. For example, an autopsy series from the National Cancer Institute showed that 38 of 56 patients with FL (~70%) had histological transformation at autopsy.[12] This suggests that transformation is a biological event inherent to the natural history of FL.

Three large studies, each having a median follow-up of at least 9 years, show a consistent risk of transformation of about 30% at 10 years after the initial diagnosis of FL.[9,10,13] The Bastion study of 220 patients with FL (with TL defined by either pathological or clinical criteria) showed a 22% and 31% transformation rate at 5 and 10 years, respectively.[10] The probability of transformation in this study was relatively constant for the first 5 years after the initial FL diagnosis; however, after 6 years, only 7 transformation events occurred in the 95 patients who remained at risk, suggesting a plateau in the incidence of transformation after 6 years.[10] In the St. Bartholomew's series of 325 patients with FL, reported by Montoto and colleagues, (with TL defined solely by pathological diagnosis) the risk of transformation at 5, 10, and 15 years was 17%, 28% and 37%, respectively.[13] Similar to that seen by Bastion and colleagues, a plateau in the incidence of TL was seen, with no increased rate of transformation being evident after 12.2 years of follow-up.[13]

The Vancouver series of 600 FL patients, reported by Al-Tourah and colleagues, (with TL defined by either clinical or pathological criteria) showed a continuous risk of transformation, at a cumulative rate of 3% per year for at least 15 years of follow-up, with a 10-year risk of 30%.[9] In contrast to that seen in the prior studies, there was no evidence of a plateau in the risk of transformation, as 16% of patients had evidence of transformation at more than 10 years of follow up.[9]

The data from these three series highlights several important issues. First, the incidence of TL by 10 years is about 30%. Second, the incidences of TL in all three studies, two of which included cases that were defined solely on clinical grounds without histologic confirmation while one required histologic confirmation, were indistinguishable.[9,10,13] This suggests that if a biopsy cannot be obtained (although every effort should be made to obtain one), it is likely the patient has TL if they have the clinical findings as defined in the Bastion and Al-Tourah series, as defined above.[9,10] This is further underscored by the findings of Al-Tourah and colleagues that (a) all patients with pathologically confirmed TL (except one) met the clinical definition for TL, and (b) the outcome of the patients with TL defined clinically were similar to that of the patients defined pathologically.[9]

As to whether the risk of transformation decreases with time is not clear. Indeed, similar to the report of the Vancouver group, there was no clear evidence that a plateau in the transformation risk was seen either in the group of FL patients who were initially observed or the group of FL patients who had initial treatment in the seminal series from Stanford as reported by Horning and colleagues.[14,15]

What Is the Underlying Biology of Transformation?

The physiology of the malignant FL follicles appears to recapitulate at least some of the functions of normal lymph node follicles, specifically the ongoing somatic hypermutation and immunoglobulin (Ig) class switching that are critical for the generation of the vast antibody diversity needed for survival. Somatic hypermutation is driven by activation induced deaminase (AID). In FL, the process of somatic hypermutation is ongoing, resulting in point mutations and small deletions/insertions within the Ig loci so that FL cells produce progeny with Ig heavy and light chain sequences that are slightly altered. As such, FL appears to be comprised of a large number of related subclones, all vying for predominance. Indeed, some reports

show such high rates of ongoing somatic hypermutation that the probability of any two malignant B cells derived from the same specimen of having different Ig sequences is at least 50%. A number of papers have shown highly complex "family trees" in FL, in which it is possible to identify the most likely sequence of the "founder" or common progenitor cell. Based on these Ig and proto-oncogene sequencing studies, it is likely that the transformation of FL to DLCL may be a result of either divergent evolution from a progenitor cell common to both the FL and the DLCL and/or by direct evolution from the FL clone.[16]

Finally, the mechanisms that drive the physiological somatic hypermutation and class switching seen in normal germinal center (GC) B cells place a "genotoxic stress" on these B cells, which may result in the emergence of GC B cell–derived neoplasms, such as FL, and may further result in the transformation of FL to DLCL. Taken together with that described above, the normal physiological processes of somatic hypermutation and class switching in GC B cells, driven in part by AID, may create an environment favorable for molecular events that result in the generation of both FL and TL.

What Are the Molecular Events Associated with Transformation?

Several recent studies have attempted to identify molecular lesions that drive transformation using paired low-grade and transformed specimens from individual patients.[17-20] One of the largest such series was reported by Davies and colleagues, who performed gene expression profiling (GEP) on 20 paired FL/TL specimens.[18] They found that TL generally has an expression pattern most similar to GC-type DLBCL. In addition, the genes most commonly up-regulated in the TL specimens were those related to proliferation. Lesions of TP53, CDKN2A, and c-REL were found only in those cases with higher proliferation signatures.[18] There was also a clear relationship between c-MYC expression levels and the proliferation signature.[18] These data suggest that one pathway of transformation is associated with high proliferation and the presence of well-defined oncogenic molecular abnormalities, while another pathway is independent of such an increase in proliferation related genes.

The technique of comparative genomic hybridization (CGH) has also been applied to paired specimens by Fitzgibbon and colleagues, and has shown acquired changes in the chromosome copy number (aCNA) with transformation.[19] This same study used single nucleotide polymorphism (SNP) analyses to discover regions with loss of homozygosity that occur in the absence of changes in copy number.[19] Such homozygosity, called acquired uniparental disomy (aUPD), is thought to occur through mitotic recombination or non-disjunction and may result in a cell becoming homozygous for a preexisting abnormality that now gives the cell a growth advantage. Consistent with all prior studies using standard karyotypic analysis, these types of genetic lesions were found to be more abundant in TL compared with FL. aUPD was detectable in 65% of samples, suggesting that this is an extremely common mechanism for genetic damage in FL. The study also implicated aUPD in specific lesions having plausible roles in transformation. For example, aUPD rendered three TL cases homozygous for pre-existing mutations in the cyclin-dependent kinase inhibitor 2A (CDKN2A) and the tumor protein 53 (TP53).[19] As mutation, hypermethylation, and deletion of both these genes have been previously associated with transformation, this work now adds aUPD to the list of mechanisms that may affect these loci. This study also showed that in some cases, the aUDP pattern in the FL sample was maintained in the TL sample, suggesting direct evolution of the TL from the FL; in the majority of sample pairs, however, the abnormalities in the FL sample were absent in the TL sample, suggesting the possibility that both the FL and TL arose by divergence from a common precursor.[19]

O'Shea and colleagues evaluated 182 FL cases for SNP and copy number using these same methods, and confirmed that large portions of the FL lymphoma genome are often affected by aUPD.[21] Of particular interest was that an aUPD on chromosome 16p, which occurred in 22 of 186 specimens, correlated with a poor event-free survival (EFS), which remained significant after adjusting for the IPI score, and was specifically predictive of transformation.[21] Taken together with the data presented above, aUPD likely plays a role in the transformation process.

Finally, a range of other molecular parameters have been associated with transformation, including TP53 expression,[22,23] microRNA profiles,[24] hypermethylation of the CDKN2A gene,[25] altered expression of c-myc and its regulated genes,[26] p38 MAP kinase dysregulation,[27] 5′ bcl-6 mutations[28] and aberrant somatic hypermutation.[17,20] Despite these molecular events being associated with transformation in some cases, they are not consistent findings among TL samples. This suggests that multiple alternative mechanisms are likely involved in the pathogenesis of TL.

The Role of the Tumor Microenvironment in Transformation

A seminal GEP study from the Leukemia Lymphoma Molecular Profiling Group showed that the immunological microenvironment of FL is a critical factor that is predictive

of patient outcome.[29] It is therefore not surprising that the type of interaction FL B cells have with other immune-effector cells within their microenvironment would affect the transformation risk. Glas et al looked at GEPs of the initial diagnostic FL biopsy specimens of patients who either (a) subsequently had histological transformation to DLCL (within 3 years from the initial FL diagnosis), or (b) had no subsequent clinical or pathological evidence of transformation.[30] Greater then 60% of the genes that were discriminative between these two groups encoded for proteins involved in cellular immunity and inflammation. Indeed the GEP from those patients destined for transformation were similar to the GEP from reactive hyperplastic nodes.[30] In contrast, the GEP from patients who did not transform showed a down-regulation of immune-related genes, similar to what would be anticipated from non-activated lymphoid tissue. This suggests that an "immune-activated" status at diagnosis of FL may somehow be predictive for, and involved, in the pathogenesis of transformation. This was further evaluated by using immunohistochemistry techniques.[30] Indeed, the T-cell activation state was higher in the samples from patients destined for transformation compared with samples from those who did not transform, as determined by the expression of the activation marker CD69.[30] In addition, the spatial relationships of the immune-effector cells were critical; $CD4^+$ T cells were found within the neoplastic follicles with or without an interfollicular component in the samples from patients destined to transform, whereas the $CD4^+$ T cells were found predominately between the follicles in the samples from patients who did not transform.[30]

Although there were no differences seen in this study in the numbers or spatial relationships of regulatory T cells (Tregs, which suppress effector T-cell function) between the two groups, Farinha and colleagues have recently shown that a perifollicular localization of Tregs was associated with an increased risk of transformation.[31] Furthermore, Carreras and colleagues have shown that high numbers of Tregs are associated with improved survival in patients with FL and the numbers of Tregs decrease during transformation.[32] Carreras and colleagues have also recently shown that FL having high numbers of T cells expressing programmed cell death-1 (PD-1), a member of the CD28 family of membrane receptors that attenuates T-cell activation, have a good prognosis.[33] In contrast, patients with low numbers of PD-1 positive T-cells (a population distinct from Tregs) had a higher incidence of transformation.[33] Taken together these data support a pivotal role of the immune response in the transformation process.

How the tumor micro-environment could affect transformation is highly speculative. It is likely, however, that T cells either support or inhibit the transformation process, dependent on which T-cell subset is interacting with the FL cells. For example, in normal lymph nodes, GC helper T cells provide "help" to GC B cells, supporting their survival and driving their expression of AID. In contrast, intrafollicular Tregs may inhibit such GC helper T cell–B cell interactions.[34] Furthermore, effector T cells may elicit immune responses against normal GC B cells, FL cells, or even TL cells, but effector T-cell priming and cytotoxicity is inhibited by Tregs. Whatever the immunological processes are, it is clear that the tumor microenvironment plays a critical role in the transformation process, and a better understanding of this role may lead to immunologically targeted approaches to prevent transformation.

Are There Clinical Variables at the Time of the Initial Diagnosis of FL that are Predictive of Transformation?

The variables predictive of transformation differ among the reported studies due in part to differences in how TL was defined, the variables examined, and the FL treatments employed. However, a general theme emerges from these studies that factors typically associated with poor outcome for patients with FL are predictive for transformation. For example, advanced stage at diagnosis, high International Prognostic Index (IPI) or Follicular Lymphoma International Prognostic Index (FLIPI), high β_2 microglobulin, and low albumin have all been associated with an increased risk of transformation in univariate analyses.[9,10,13,35] In addition, patients not achieving a complete remission (CR) after initial FL therapy had a higher risk of transformation.[10] In addition, those patients who required at least 2 courses of treatment to manage their initial FL had a higher risk of transformation compared to those that required no treatment ("watch and wait") or only one course of treatment to manage their initial FL.[9] This association of the treatment sensitivity of the initial FL to risk of transformation is of particular interest, as some of the molecular events associated with transformation, such as lesions of p53, are also associated with chemotherapy resistance.

A critical question is whether the transformation risk is altered by treating patients early after the diagnosis of FL is made, or by observing them in a "watch and wait" approach. Data from Stanford show an equal transformation risk in those patients for whom therapy was deferred and those whom were treated at diagnosis.[14,15] Similarly, the Vancouver group found no difference in transformation risk between the 407 patients treated at diagnosis with chemotherapy, the 90 patients treated initially with radiation therapy, or the 103 patients initially observed without therapy.[9] In contrast, in the St. Bartholomew's series, those patients initially observed, without having treatment at

diagnosis, had a higher incidence of transformation than those treated at diagnosis.[13] As the authors acknowledge, this is somewhat counterintuitive. The authors suggest that one possible difference in their analysis, compared with that of the Stanford group, was that the risk of transformation in the group of "watch and wait" patients at Stanford may have been underestimated, as fewer of those patients underwent a biopsy at the time of progression then did the patients that were initially treated.[14,15] The total body of evidence, however, does not support the premise that early treatment of FL results in a decreased risk of transformation compared with those patients that are initially observed. In addition, there is no clear evidence that the risk of transformation is altered by the type of initial therapy given for the FL. Whether all of this will still be the case in the rituximab era is not yet known.

What Is the Outcome for Patients with TL?

The overall outcome for patients with TL in most series is poor; the median duration of survival after transformation generally ranging from 1 to 2 years, with most deaths being due to lymphoma.[9,10,13-15,35] The adverse effect of transformation on patient survival is further illustrated by the findings of the Vancouver group, where the 10-year OS for patients with non-transformed FL was 75%, whereas only 36% of the TL patients were alive 10 years from the time of their initial FL diagnosis.[9] Similar findings were also seen in the St. Bartholomew series.[13]

Are There Clinical Prognostic Factors at the Time of the TL Diagnosis that Are Predictive of Outcome?

The clinical and laboratory findings at the time of transformation associated with a worse OS are high LDH, advanced-stage disease, having had no prior CR, or having had no response to salvage chemotherapy.[9,10,13] Despite the overall poor outcome of patients with TL, a subset of patients having a relatively good outcome was identified by Yuen and colleagues at Stanford.[36] Seventy-five patients with pathologically confirmed TL from 1965 through 1988 were evaluated.[36] Using a Cox regression analysis, the variables significant for survival after transformation were stage (limited vs extensive), prior chemotherapy (none vs any) and response to treatment after transformation (CR vs PR vs NR).[36] Limited disease at transformation had a particularly favorable outcome. Those having limited stage disease who achieved a CR had a better OS than those with advanced-stage disease who achieved a CR (108 vs 18 months).[36] A similar superior outcome for patients having limited-stage disease at transformation was seen in the Vancouver series, the 5-year OS being 66% for those with a limited transformation compared to 19% for those with advanced-stage at transformation ($P < .001$).[9] Finally, a recent study by Tan et al demonstrated a superior OS for patients who were chemotherapy naïve at the time of transformation compared with those patients who were previously treated.[37]

What Treatment Approaches Have Been Evaluated in TL?

High-dose Therapy and Autologous Stem Cell Support (ASCT)

The data supporting the efficacy of this approach for patients with TL are limited, as most studies include only small numbers of patients and the median follow-up of patients in these studies are quite variable.[38-46] In addition, most of these studies were done in the pre-rituximab era. Despite these limitations, both registry and phase II data (**Table 1**) suggest a potential benefit to autologous transplantation for a proportion of patients with TL, with some patients experiencing long-term benefit.[38-46] The largest series is based on registry data from the European Bone Marrow Transplant Registry (EBMTR) of 50 patients with TL.[42] With a median follow up of approximately 5 years, the median progression-free survival (PFS) was 13 months, with a 5-year OS and PFS of 51% and 30%, respectively. The major cause of treatment failure for these patients was relapse (50%). However, the treatment-related mortality (TRM) of 18% in this series was higher than that typically seen with autologous transplantation.[42] When the survival of these patients was compared to that of matched patients with low-grade, or *de novo* intermediate or high-grade lymphoma in a case-matched analysis, there was no difference in OS or PFS between these groups, although the median PFS of the patients with *de novo* lymphoma was 23

Table 1. Autologous transplant series for transformed lymphomas (TL).

Study	N	Median follow-up, y	OS	PFS/EFS	TRM, %
Williams[42]	50	4.9	2 y: 64% 5 y: 51%	5 y PFS: 30% Median PFS: 13 mo	18
Chen[40]	35	4.3	5 y: 37%	5 y PFS: 36%	20
Ramadan[46]	33	1.7	2 y: 72% 5 y: 72%	2 y EFS: 47% 5 y EFS: 33%	10
Friedberg[38]	27	3.0	5 y: 58%	5 y DFS: 46%	0
Foran[45]	27	2.4	Median: 8.5 y	N/A	15
Sabloff[44]	23	7.6	5 y: 56%	5 y PFS: 25%	4
Andreadis[43]	22	5.5	Median: 4.6 y	Median EFS: 1.4 y	4

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

months compared with 14 months in the TL group.[42] Other studies show 5-year OS rates ranging from 40% to 70% and 5-year EFS or PFS ranging from 25% to 36%.[38-46] Secondary myelodysplastic syndromes and acute myeloid leukemias occurred in 7% to 15% of patients.[38-46] Given the overall poor prognosis of patients with TL however, high-dose therapy with autologous stem cell support is a viable therapeutic option.

Allogeneic Transplantation

Given the high relapse rate seen with autologous transplant, and the potential benefit of a graft-versus-lymphoma effect (GVL) inherent in allogeneic transplant, there has been recent interest in exploring the role of allogeneic transplantation for patients with TL. The largest series was a population-based study by Ramadan and colleagues that reported the outcome of 40 patients (25 with TL and 15 with discordant/composite lymphoma) undergoing a myeloablative allogeneic transplantation (1 patient had a reduced-intensity transplantation).[47] The 36% TRM at 3 years was substantial. In addition, the 42% relapse at 5 years was high. The 2-year and 5-year EFS were 36% and 23%, respectively, and OS were 39% and 23%, respectively. In addition, 84% of the surviving patients had extensive chronic GVHD. Because of both the high TRM and relapse rate for patients undergoing a myeloablative allogeneic transplantation, the outcome for patients with TL undergoing autologous transplantation was superior to that of the allografted patients with TL in this same population-based group.

In order to decrease the morbidity and TRM of myeloablative allogeneic transplants, non-myeloablative allogeneic transplant (NMA) approaches have been studied and indeed have been found to be effective for a number of hematological malignancies. Rezvani and colleagues reported on 16 histologically confirmed patients with TL who underwent an NMA.[48] The 3-year PFS and OS was poor, 21% and 18%, respectively. The outcome for these patients with TL was significantly worse than that of patients with non-transformed FL (n = 54), who had a 3-year PFS and OS of 43% and 52%, respectively. The 3-year non-relapse mortality (NRM) for all patients was 42%.

TL can have an aggressive clinical course and as such there may not be sufficient time for GVL to develop after an NMA, perhaps explaining the relatively poor outcomes seen with this approach. While there are contradictory reports, two recent studies, however, have shown a benefit of NMA for patients with aggressive lymphomas including TL.[49,50] Thomson and colleagues reported on 48 patients with relapsed/refractory DLCL treated with an alemtuzumab-containing NMA regimen, 18 of whom had transformed disease.[50] With a median follow-up of 52 months, the 4-year NRM for the entire group of patients was 32%, with the 4-year OS and PFS for the patients with TL being 60% and 61%, respectively.[50] Despite this promising data, allogeneic transplantation cannot be considered a standard approach for patients with TL, and this approach should be limited to clinical trials.

Radioimmunotherapy

Radioimmunotherapy (RIT), using monoclonal antibodies labeled with a radioactive nuclide, has been shown to have significant activity in patients with FL, and indeed two such agents, yttrium Y^{90} ibritumomab (Zevalin) and iodine I^{131} tositumomab (Bexxar), are available for patients with relapsed or refractory lymphoma. RIT has also been shown to be of benefit for the small number of patients with TL studied, as shown in **Table 2**.[51-55] The largest series of patients was reported by Zelenetz and colleagues, who evaluated the efficacy of RIT in 71 patients with TL compiled from five I^{131} tositumomab studies.[55] The median age of these patients was 59 years; 70% had disease > 5 cm; the median number of prior therapies was four (range 1-11); and 52% had an IPI score of ≥ 3. Seventy percent of these patients had DLCL and 20% follicular large cell lymphoma

Table 2. Radioimmunotherapy (RIT) series for transformed lymphomas (TL).

Study	Agent	N	Response rate, %	Median duration of response, mo. (95% CI)	CR/Cru, %	Median duration of response for CR/CRu, mo (95% CI)
Kaminsky [53]	I^{131}	14	79	13.9	50	–
Vose [51]	I^{131}	10	60	12.1 (4.5-NR)	50	14.3
Davies [52]	I^{131}	7	71	41.0 (4-NR)	29	NR
Witzig [54]	Y^{90}	9	56	N/A	N/A	N/A
Zelenetz [55*]	I^{131}	71	39	14.7 (10.8-40.8)	25	36.5 (14.4-59.1)

I^{131} indicates iodine I^{131} tositumomab (Bexxar); Y^{90}, yttrium Y^{90} ibritumomab tiuxetan (Zevalin); mo., months; 95% CI, 95% confidence interval; NR, not reached; CR, complete response; Cru, complete response unconfirmed; N/A, data not available
*compilation of data from 5 iodine I^{131} tositumomab (Bexxar) studies

at transformation, all having had an initial diagnosis of an indolent lymphoma.[55] The overall response rate was 39% with a median duration of response of 14.7 months (95% confidence interval [CI] 10.8-40.8 mo). For the 25% of patients having a confirmed CR, the median duration of response was 36.5 months (95% CI 14.4-59.1 mo). Indeed, 24% of all patients had a response lasting longer than 12 months.[55] RIT therefore has clear activity in patients with TL and is an effective, well tolerated therapeutic option for such patients. To date, I^{131} tositumomab is the only RIT agent approved by the FDA for patients with TL.

New Agents

Despite the plethora of new agents being studied for patients with NHL, there is a paucity of data on the efficacy of these agents, specifically in patients with TL. One such new agent, however, deserves mention. The efficacy of the novel alkylating agent bendamustine was evaluated by Friedberg and colleagues in 15 patients with rituximab-refractory TL.[56] In their series, 13% had a CR/Cru and 53% had a PR.[56] The median duration of response, however, was only 2.3 months (95% CI, 1.7-5.1).[56] Further studies to determine the optimal agents to combine with bendamustine so to further increase its activity in patients with TL are warranted.

Management of Patients with TL

The optimal therapeutic strategy for patients with TL has not been well defined in the context of prospective clinical trials, and as such there is a need both to develop such trials and to enroll patients with TL on such trials. Despite this, several possible approaches can be considered:

1. If the patient had either no prior therapy for their initial FL, or had treatment with a non-anthracycline containing regimen, rituximab-CHOP (R-CHOP) should be considered, given the excellent outcome seen with this regimen for patients with *de novo* DLCL. Furthermore, similar to what has been shown for *de novo* DLCL, the addition of rituximab to CHOP has been shown to improve the survival of patients with TL.[57] If the patient has a CR to such a regimen, one can consider consolidating the response with either RIT or an ASCT, although whether this is better than observing such patients and reserving RIT or ASCT to the time of relapse is not known. If the patient has a PR to R-CHOP, then consideration should be given to RIT or ASCT. For those failing R-CHOP, RIT or other palliative approaches can be considered, as can an attempt to induce a response with standard salvage regimens and, if successful, proceed to ASCT.
2. If the patient has localized transformation, data from Stanford suggest that involved field radiotherapy (IFXRT) may have benefit for such patients.[36] If the patient has not had prior anthracycline chemotherapy, then one should consider a combined modality approach, using R-CHOP followed by IFXRT.
3. If the patient has had prior anthracycline exposure, then one can give consideration to RIT alone or to a standard salvage regimen, such as R-ICE, followed by an ASCT.
4. Given the questionable efficacy and the high morbidity and mortality of allogeneic transplantation for TL, this approach should only be considered in the context of a clinical trial.

Epilogue

In this chapter we reviewed recent data on the incidence, natural history, biology and treatment of TL. The big unknown in all of this is whether rituximab, which is now universally used as part of the initial treatment approach for patients with FL, will alter the incidence, natural history and biology of transformation. In another words, will transformed lymphomas even be a topic for an educational session 3 or 4 decades from now?

Disclosures

Conflict-of-interest disclosure: SHB is a consultant for Millennium, Enzon, and Genentech and is on the Genentech speakers bureau. WRB declares no competing financial interests.
Off-label drug use: None disclosed.

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