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Management of Patients With Histologic Transformation

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Abstract

The incidence of histological transformation is up to 30% over a period of 10 years. This risk persists even beyond the initial decade of diagnosis of an indent lymphoma. In this era of emerging novel therapies, one could hope for an improved survival. There are currently no randomized trials guiding therapy for transformed lymphoma. Treatment recommendations are based on observational studies or non-randomized single arm clinical trials. To that extent, although routinely recommended and performed at transplant centers, voluminous evidence to suggest the timing or type (autologous or allogeneic) of transplant is lacking. In this article, we discuss the clinical features, treatment approach and role of stem cell transplant in transformed lymphoma.

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Introduction

A diagnosis of follicular (grade 1-2) lymphoma (FL) followed by a transformation to an intermediate (diffuse large B-cell [DLBCL]) or an aggressive (Burkitt) lymphoma is referred to as histological transformation (HT). Occasionally, there is 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] This article does not include discussion of Richter transformation, which is HT of chronic lymphocytic leukemia to DLBCL. The 2016 World Health Organization classification of lymphoid malignancies includes a new entity concerning transformation: T-cell histiocytic-rich B-cell lymphomalike transformation of nodular lymphocyte—predominant Hodgkin lymphoma, which portends a more aggressive clinical course, unlike nodular lymphocyte—predominant Hodgkin lymphoma, and requires an aggressive approach.[2]

The natural history of FL has been influenced in the era of monoclonal antibody (mAb) therapy, and the true risk of HT appears to be 10% to 15% over 5 years. Previous studies report that the HT of an indolent follicular lymphoma to a high-grade lymphoma occurs at a rate of 3% per year. The prognosis for HT is generally poor, with rapid progression of the disease. Most of these studies, however, were conducted in the pre—anti-CD20 monoclonal antibody era and report 5-year survival rates of 55% to 65% for early-stage and 15% to 25% for late-stage disease.[3-5] Young patients with limited-stage chemosensitive disease experience prolonged survival. This group accounts for <20% of all HTs.[5]

Standard chemotherapy and radioimmunotherapy have offered promising responses; however, the duration of response does not appear to last long.[6] Several studies evaluating the role of autologous stem cell transplantation (auto-SCT) as a salvage regimen have indicated that a subset of patients benefits from this modality of treatment.[7] With an improvement in supportive care, outcome after allogeneic stem cell transplantation (allo-SCT) has improved significantly over the past decade.[8] Successful results have been reported in selected patient populations that have achieved long-term disease-free survival after allo-SCT.

Genetic Mutations and Cell of Origin in HT

The characteristic translocation (14;18)(q32;q21) that is the hallmark of follicular lymphoma arises in early B cells and is critical for FL pathogenesis. Subsequent accumulation of oncogenic mutations via the mistargeted enzyme activation-induced deaminase (AID) that leads to somatic hypermutation of immunoglobulin loci has been implicated as a cause for transformation. BCL2 mutations correlate with AID expression and have been shown to be associated with a shortened time to transformation.[9] Multiple mechanisms leading to cell-cycle alteration appear to drive HT. Epigenetic dysregulation in MLL2, EZH2, and CREBBP that control the

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chromatin structure contribute to dysregulated cell growth via cyclin-dependent kinase (CDKN2A) and DNA damage by interfering with the p53 pathway.[10,11]

In most patients, HT arises from a germinal center subtype, although a significant proportion of cases (16%) is of the activated B-cell (ABC) subtype as determined by the Lymph2Cx gene-expression assay. The absence of BCL2 translocation favors an ABC-subtype of transformation. Similarly, expression of IRF4 (interferon regulatory factor family) that regulates germinal center cell formation was associated with a non−germinal center type of transformation.[12,13]

Tumor Microenvironment and HT

The underlying biology of transformation is not fully understood. Gene-expression profiling (GEP) of 20 paired samples of FL and HT performed by Davies et al,[14] noted 2 pathways by which HT may evolve. One is via a similar proliferation rate as that of the preceding FL and the other set overexpressed genes associated with proliferation signatures, suggesting that an acquired high-proliferation rate underlies transformation. The acquisition of novel mutations via somatic hyper mutations also has been implicated in the pathogenesis of HT.[14,15] Importantly, it has been suggested that the tumor microenvironment may play a crucial role in transformation. In a study by Glas et al,[16] GEP signatures were performed on FL samples of patients who later had transformation or had no subsequent transformation. The GEP of patient samples that did not transform had a downregulation of the immune-related genes, therefore implying that the transformation may be mediated by an "immune signature." There was also an overexpression of CD69, which is an activated T-cell marker in samples that were destined to transform.[16] Also, perifollicular localization of T-regulatory cells (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.[17-19] A high degree of intrafollicular infiltration of CD68+, PD-L1+ macrophage, and CD4+ T cells was associated with a shorter time to transformation.[20]

These findings suggest that the tumor microenvironment and the mutated oncogenic pathways of the malignant cell contribute to HT, and therefore targeting multiple pathways and sites is essential in the treatment of HT.

Clinical and Radiological Features in HT

Several studies have reported various risk factors that are associated with transformation. The following features at initial presentation of FL have a relatively high likelihood of HT: advanced stage (III/IV), increased serum lactate dehydrogenase (LDH), elevated B2-microglobulin, grade 3 histology, high FL international prognostic index score, >1 extranodal site, systemic B symptoms, Eastern Cooperative Oncology Group score >1, and lack of complete response following initial therapy.[4,21-23]

The clinical features that raise the suspicion of transformation include the following: rapid, discordant nodal growth; sudden rise in LDH; new-onset hypercalcemia; or unusual extranodal involvement, such as liver or bone. When transformation is suspected, an excisional biopsy is strongly recommended to allow sufficient sample availability for complete characterization of histologic and immunologic classification. As previously mentioned, although transformation to DLBCL is most commonly encountered, rare transformation to Burkitt lymphoma also has been reported. Pathology review is therefore crucial for treatment planning. Radiological imaging, such as positron emission tomography with fludeoxyglucose (FDG-PET)/computed tomography may help guide the biopsy site. A few prospective studies with a small number of patients suggest a direct correlation between the standardized uptake value (SUV) and the specificity of suspected transformation. Among patients with an SUV_{max} of >17, the positive predictive value of FDG-PET for detecting HT was 100%, whereas patients with an SUV_{max} of 10 to 14 had a specificity of 80% to 94% for HT, respectively.[24-26] In the absence of clinical features, over-reliance on SUV_{max} in newly diagnosed FL is not recommended. In situations in which obtaining a biopsy is not feasible due to accessibility, and the clinical suspicion of HT is high, treatment directed toward an aggressive histology is recommended.

Outcomes of Transformed Lymphoma in the Anti-CD20 Antibody Era

There is modest evidence that survival following HT has improved in the anti-CD20 mAB era. The 5-year risk of incidence of HT has been reported to be 10% to 12% in the mAb period. It is unclear if early detection with the implementation of FDG-PET has had an influence on improved outcome. Three large observational studies reported in the mAb era have shed light on the outcome of patients with HT. Analysis of outcomes on 118 patients from the National Comprehensive Cancer Network database reported a 2-year survival of 68%. In patients 60 years or younger who underwent autologous stem cell transplantation, the 2-year overall survival (OS) was 74% versus 59% for those who did not receive a transplant. In this study, younger patients who did not receive any chemotherapy before transformation had a 100% 2-year survival even without transplantation. It should, however, be noted that there were only 5 patients (10%) in this group with a short survival follow-up time.[27] In the study reported by Link et al[28] from the Iowa/Mayo clinic experience, the OS after transformation was 50 months. The transformation rate was noted to be higher in patients who were initially observed (wait and watch) compared with those who received rituximab monotherapy. Survival was improved in patients with transformation more than 18 months after FL diagnosis (66% vs. 22%, $P < .001$).[28] This is in contrast to our experience from a transplant database, in which we reported a 5-year OS of 80.4% in patients with early transformation compared with 31.5% ($P = .018$) in patients with transformation that occurred more than a year after FL diagnosis.[29] This may be a reflection of selection bias, as the study included patients who received SCT. In the prospective study reported by Ardeshna et al,[30] in which 379 patients were randomized to watchful waiting or maintenance rituximab at initial diagnosis of FL, biopsy-proven transformation occurred in 11% in the watchful waiting group and 7% in the maintenance rituximab group ($P = .19$), suggesting no increased risk of transformation in patients who were initially observed. In the third large outcome study by the national Lymphocare study, 379 patients developed transformation (pathologically confirmed and