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Supplement Article

XV. Clinical aspects of transformed lymphoma

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Introduction

As outlined in the previous sections by Dr. Gascoyne and Dr. Rossi, histologic transformation (HT) refers to the biologic events leading to development of high-grade, aggressive non-Hodgkin's lymphoma in a patient with an underlying indolent lymphoma. HT is a well-described event in the natural history and clinical course of patients with indolent lymphomas. This phenomenon has been studied most extensively in patients with follicular lymphoma (FL) and subsequent transformation to a diffuse large B-cell lymphoma (DLBCL) [1]. However, HT is not unique to FL, but has been described also in other subtypes of indolent lymphoma including marginal zone lymphoma, lymphoplasmacytic lymphoma, and lymphocyte predominant Hodgkin lymphoma and as in Richter's syndrome (RS) in small lymphocytic lymphoma/chronic lymphocytic leukemia. HT has a profound impact on the natural history of these usually indolent diseases, and the outcomes of such patients have been historically poor, although survival may be improving in the era of chemoimmunotherapy. The molecular pathogenesis of transformation of lymphoma is described in the accompanying articles, and this review highlights our current concepts of treatment as well as potential future directions of treatment for transformed lymphoma.

Much attention has focused on factors that may be used to predict diagnosis at those patients in whom HT will occur. Despite attempts to determine biomarkers and clinical characteristics that might be useful to determine this, there are few useful markers that can be used reliably to predict HT. One possible explanation for this is that recent molecular studies have made it clear that the process of HT is complex and not simply the acquisition of new molecular events within the dominant FL clone, but that HT may occur from new changes within lymphoma progenitor cells [2], or even as second primary malignancies in our patients. Whereas, we are approaching the era of more targeted therapies where we can plan treatment based upon the molecular biology of the disease and its subsequent HT, these findings have clear implications in terms of making it more difficult to identify markers within the presentation lymphoma that can potentially guide treatments in the future or predict from which subclone HT might subsequently arise.

Incidence and diagnosis of histologic transformation

The risk of HT for FL patients varies considerably in different series, ranging from 24% to 70% overall [3], and ~30% at 10 years [4]. This may be explained by differences in the patient populations studied, the length of follow-up, and the diagnostic method. A continuous risk of 3% per year was reported from British Columbia Cancer Agency (BCCA) [5], with a very similar incidence in our own patient at Barts [4]. Although it has been suggested that the incidence might decrease in the rituximab era, in a prospective observational study of over 600 patients, HT occurred in 11% of patients at a median follow-up of 5 years, and was estimated to occur at 2% to 3% per year, very consistent with the rates observed in earlier studies [6]. This suggests that incorporation of rituximab might not prevent the risk of subsequent HT. The risk of HT in other types of indolent lymphoma appears lower than that in FL. The risk of HT in patients with nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is in the order of 10% at 10 years. In large single center studies of small lymphocytic lymphoma/chronic lymphocytic leukemia patients, RS was demonstrated either by biopsy or fine-needle aspiration in 4% of patients, whereas transformation to Hodgkin lymphoma was even rarer, occurring in 0.4% of patients [7].

Diagnosis of histologic transformation

Whereas the definition of HT in patients diagnosed with a previous indolent lymphoma appears straightforward, review of the literature is confounded by the fact that different series define HT in different ways, including by histologic analysis, by fine-needle aspiration, or on clinical grounds alone [3,5,8]. Establishing HT by biopsy is clearly the diagnostic gold standard, and suspicion of HT should be verified, whenever possible, by excisional biopsy or by a good sized core biopsy and not by a fine-needle aspirate. Since patients can relapse after salvage therapy with either the original low grade histology or with transformed disease, repeat biopsy after each subsequent progression is recommended. In a population based study that included patients up to 60 years of age, more than one-thirds were diagnosed with HT on clinical grounds only [5]. Clinical features of HT include a rise in lactate dehydrogenase (LDH), presence of B symptoms, hypercalcemia, a rapid localized nodal growth or new extranodal sites of disease [3,5,6]. These features should trigger subsequent investigations to rule out possible HT. Of note, survival after transformation of patients diagnosed based on clinical criteria alone was very comparable to that of patients with histologically proven biopsy diagnosis of HT based, supporting the reliability of clinical criteria to diagnose transformation. An alternative explanation is that acceleration of disease in indolent lymphomas producing such symptoms even in the absence of documented HT also has a negative impact on prognosis; and ongoing studies are examining whether molecular changes can be seen in such patients to explain the change in clinical characteristics.

Several studies have reported on the clinical utility of an [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) scan to detect HT. There is a correlation between higher standardized uptake value (SUV) on a FDG-PET and more aggressive histology [9], and the higher the SUV, the higher positive predictive value of FDG-PET for detecting HT.[10] On the other hand, because there is a wide range of SUVmax in biopsy-proven sites of transformation [9], FDG-PET is not likely to replace biopsy as the gold standard to diagnose HT, but will remain useful in directing optimal sites for biopsy.

Clinical risk factors for histologic transformation

The risk of HT in FL is higher in those with high Follicular Lymphoma International Prognostic Index (FLIPI), and adverse clinical factors, including advanced age and LDH that are components of the FLIPI, have also been shown to confer higher risk independently [4,6,8]. The impact of treatment on the subsequent risk of transformation is more difficult to discern. Whereas studies from BCCA have suggested that more aggressive treatments including the inclusion of anthracyclines and the use of maintenance rituximab were associated with a lower risk of HT, this was not supported in other studies [8]. The impact, if any, on the introduction of early treatment on subsequent risk of HT is also controversial, as this has been shown to decrease the risk of HT in some, but not other studies [5,11]. In a randomized study of early treatment with rituximab versus continued observation, there was no difference in the risk of HT, but follow-up of this study remains very short [12].

Outcome after histologic transformation

The prognosis of patients with FL who develop HT is extremely poor with a median overall survival (OS) after transformation of 1–2 years [5,8], and the OS of patients who develop HT at any point during the course of the disease is significantly shorter than those who never undergo HT [4,5]. Among the most crucial factors in determining outcome after HT is response to therapy, and patients who achieve complete response have better outcome. Factors associated with improved outcome in patients with HT include early stage FL, use of combination chemoimmunotherapy, and patients who are chemotherapy naive at the time of HT [5,13]. It is also not clear to what extent the time to develop HT impacts outcome, but in one study, early development of HT was associated with a significantly worse outcome compared with later HT [6].

The outcome of patients with lymphoplasmacytic lymphoma whose disease transforms to DLBCL, and CLL who develop RS is universally poor, with a median OS of 8–16 months [14]. The outcome of patients with NLPHL with transformation to DLBCL is significantly better, with the 10-year survival after transformation being reported at 60% [15].

More recent studies have suggested that outcome might be improving in the era of chemoimmunotherapy [16], and in one study, the outcome of HT patients treated with R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone) with HT was similar to that seen in patients with primary DLBCL [6].

Management challenges and future directions

The treatment approach for a patient with HT is often individualized, and there have been no randomized studies in the modern era that can be used to guide practice. Patients with HT are usually excluded from participation

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in clinical trials, further confounding the pool of data on which we can make clinical decisions. There is therefore no standard therapy for HT, and treatment decisions are often based upon previous treatments received and duration of previous response. The historically poor prognosis of patients with HT has prompted many centers to adopt high-dose therapy (HDT) and autologous stem cell transplant (ASCT) as standard treatment to improve outcome in these poor risk patients. Most transplant studies conducted in the pre-rituximab era have been small retrospective studies, but registry data suggest that the outcome after ASCT for HT is similar to that of non-transformed lymphomas [17]. A problem with interpretation with studies of outcome after transplant is that studies report the outcome from the time of transplant and we usually do not know the denominator to determine what proportion of patient actually get to transplant.

The continued role of ASCT in the rituximab era also remains largely an unanswered question. ASCT appears to improve outcome only modestly compared with rituximab-containing chemotherapy regimens [18]. Multivariate analysis of registry data showed no clear impact of pretransplant rituximab, but patients in the National Comprehensive Cancer Network database undergoing ASCT after previous rituximab had superior outcome than those treated with chemotherapy alone, or to those who underwent ASCT prior to the introduction of rituximab [18]. On the other hand, patients who are rituximab naive prior to ASCT appear to have better outcome than those with prior rituximab exposure, paralleling observations in DLBCL patients undergoing ASCT.

The role, if any, of allogeneic SCT is even more difficult to discern with very few patients reported from which to make meaningful conclusions. In one small study, no difference was seen in the outcome of patients undergoing ASCT or allogeneic transplant [19]. For HT relapsing after ASCT, further salvage therapy with allogeneic SCT may improve outcomes but at a cost of significant treatment-related mortality.

Practical management of patients with histologic transformation

When HT is suspected on clinical grounds, excisional or core biopsies and not fine-needle aspirates are indicated, and PET scan may be useful in guiding sites of biopsy in those areas with high SUV. Treatment naive patients should be treated with R-CHOP, and these patients may have good outcome but there is no data on the utility of maintenance rituximab in this setting. Patients who have received prior treatment but have not received prior anthracycline for FL should also receive R-CHOP chemotherapy. Those patients who have already received R-CHOP for FL are candidates for platinum based salvage chemoimmunotherapy, and if they are fit enough for this approach, should then be considered for consolidation with HDT and ASCT if they have good response. The management of elderly patients who develop HT late in their disease course remains a major challenge.

Future directions

Most patients with HT are excluded from clinical trials, so there is limited data on the use of novel agents in this disease setting. However, there is an ever increasing number of agents, which are being explored in indolent and aggressive lymphomas, including lenalidomide, ibrutinib, idelalisib, BCL2 inhibitors such as GDC-0199/ABT199, anti-programmed death-1 (PD-1) monoclonal antibodies, and EZH2 inhibitors. These agents are being studied alone and in combination, and these may have some potential in patients with HT. Improvements in our understanding of the molecular pathogenesis of HT should lead to more rational targeted approaches to manage patients with HT.

Conflict of interest

The authors have no competing interest.

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