

What's New in Histological Transformation of Indolent Lymphomas?

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The understanding of the molecular pathogenesis of non-Hodgkin's lymphomas (NHL) has significantly improved in recent years. Advances in molecular biology and genetics lead to the identification and characterization of several oncogenic pathways involved in lymphomagenesis. This knowledge will ultimately lead to improved diagnostic and therapeutic strategies for patients with NHL (1).

The evolution of indolent lymphomas to aggressive histology, known as histological transformation, is a frequent occurrence for all subtypes of low grade B cell lymphoproliferative disorders (2).

Histological transformation to an aggressive lymphoma is a well-described event in the natural history and clinical course of patients with so-called indolent lymphomas. This phenomenon has been studied most extensively in patients with follicular lymphoma.

Histological transformation of follicular lymphoma to a more aggressive non-Hodgkin's lymphomas is a pivotal event in the natural history of follicular lymphoma and is associated with poor outcome. While commonly observed in clinical practice and despite multiple studies designed to address its pathogenesis, the biology of this process represents an enigma (3).

A number of genetic aberrations found in follicular lymphoma B cells have been associated with histological transformation. An analysis of paired samples was first used to implicate mutations in p53 (chromosome 17 p) as an important genetic event underlying histological transformation of follicular lymphoma.

Gene expression studies of paired samples demonstrate that follicular lymphoma transformation is associated with changes in expression of *MYC* and its target genes. These changes could be attributed to *MYC* mutations and translocations in a small fraction of the cases, but no structural aberrations were identified in the majority of the cases. The changes in the expression of *MYC* and its targets might reflect a more general change in the expression of a primitive stem cell gene signature upon transformation. The presence of *MYC* translocations in follicular lymphoma biopsies at diagnosis is uncommon, with some studies suggesting an association with an increased risk of transformation.

Somatic mutations in either *BCL2* or *BCL6* genes have also been associated with histological transformation, while *BCL6* translocation in diagnostic follicular lymphoma specimen was suggested to predispose to subsequent transformation. More recently, genetic alterations in-

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volving chromosome 1p has been shown to be a very frequent acquired genetic alteration in follicular lymphoma and has been associated with an increased risk of transformation (3).

Even with the available clinical and molecular data, we are no closer to identifying at diagnosis those patients who are destined to transform. Indeed we cannot be certain if predisposition to histological transformation exists at the time of diagnosis or whether this tendency is confined to a rare population of follicular lymphoma cells that may be below the threshold of current detection methods, making the identification at diagnosis of patients at high risk impossible (2).

Thirty-six percent of patients were diagnosed with histological transformation based on clinical criteria, which included the presence of any of the following: a rise in the lactate dehydrogenase level, a rapid localized nodal growth, new extranodal sites of disease, the presence of B symptoms or hypercalcemia. The survival after transformation for patients diagnosed based on the above clinical criteria was comparable to that in patients diagnosed with histological transformation based on a pathologic sample, supporting the reliability of the clinical criteria to diagnose transformation.

Several studies have reported on the clinical utility of a fluorodeoxyglucose

(FDG) positron emission tomography (PET) scans to detect areas suspicious of transformation, demonstrating the correlation between a higher standardized uptake value on a FDGPET and a more aggressive histology and leading to pilot studies assessing the efficacy of FDGPET to direct the biopsy to areas highly suspicious of histological transformation. Of note, the original indolent lymphoma subtype can reappear in patients with disease progression after having responded to salvage therapy for histological transformation, emphasizing the need of repeat biopsies at each progression, even after transformation (2).

The rituximab era has been characterized by a significant improvement in the prognosis

of patients with B-cell lymphomas, but histological transformation, remains one of the most important challenges in the management of patients with indolent lymphoma, the difficulties starting with the diagnosis and definition of histological transformation, and ending with the appropriate management and treatment of the event (2).

There is no standard treatment for histological transformation, the choice of therapy depending mostly on the previous therapy. Unfortunately, patients with histological transformation are often excluded both from indolent lymphoma studies and from diffuse large B-cell lymphoma studies. Thus, most patients are treated with an anthracycline containing regimen, if they have not previously received one and with a second-line regimen for diffuse large B-cell lymphoma; otherwise. The advent of rituximab has also made a difference in the outcome of patients with histological transformation.

There are some promising data reporting response rates of 57% to 79% median/response duration of around 1 year with iodine-131 tositumomab and lenalidomide.

There is no information available on maintenance with rituximab after histological transformation.

Going forward, it is crucial to incorporate histological transformation, as a major end point in clinical trials and to include patients with histological transformation, as subject of such studies if we are to see meaningful progress in the future (2).

Several long follow-up studies have demonstrated that the overall survival of patients who develop transformation at any point during the course of the disease is significantly shorter than that in patients never diagnosed with transformation. Patients who present at transformation with limited stage have a better outcome than the rest, and it has been suggested that they might achieve a relatively long survival (2).

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