Transformed Lymphoma

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KEYWORDS

• Indolent lymphoma • Transformed lymphoma • Genetic drivers

KEY POINTS

- Transformation is a common occurrence among patients with indolent lymphoma and often carries a poor prognosis.
- Traditionally transformed lymphoma has been considered difficult to treat and associated with poor prognosis.
- Increasing knowledge of the genetic drivers of this event is leading to new therapeutic approaches.

INTRODUCTION

Transformed lymphoma is a complex syndrome that encompasses an array of different underlying low-grade lymphoproliferative conditions transforming into more aggressive disease as manifest by morphologic, clinical, and genetic features. Traditionally, transformed lymphoma has been considered difficult to treat and associated with poor prognosis. However, over the last decade, advances in chemoimmunotherapy have led to new options for affected patients and better outcomes. In more recent years, utilization of knowledge surrounding the genetic changes driving the process of transformation is leading to the development and application of novel targeted therapies. Such therapies are typically not associated with the same toxicities that have accompanied high-dose chemotherapy and stem cell transplantation (SCT) and, therefore, are often suitable for use in patients who have multiple comorbidities or are of advanced age. However, there is an ongoing unmet need for novel therapies among some patients with transformed lymphoma because many of the genetic aberrations seen converge on currently untargetable pathways, such as CDKN2A, MYC, or loss of TP53.

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This article focuses on 2 of the more common scenarios: (1) the transformation of chronic lymphocytic leukemia (CLL) to diffuse large B-cell lymphoma (DLBCL), a process known as a Richter transformation (RT); and (2) the transformation of follicular lymphoma (FL) into DLBCL. For completeness, a variety of other less common situations in which transformation is recognized are described.

RICHTER TRANSFORMATION

Predisposing Factors for Richter Transformation Among Chronic Lymphocytic Leukemia Patients: Clinical and Genetic

RT is defined as the transformation of CLL into an aggressive lymphoma, most commonly DLBCL. Cumulatively, over the natural history of patients' course with CLL, RT occurs in between 5% to 20% of cases[1] and is a well-recognized and feared complication due to its poor prognosis (when compared with de novo DLBCL or CLL alone). Importantly, this inferior prognosis seems only to apply to cases in which the DLBCL is clonally related to the underlying CLL (eg, by demonstrating a shared immunoglobulin variable heavy chain [IGVH] usage). DLBCL arising in patients with CLL in whom there is not a clonal relationship to the preceding CLL (up to 20% of cases) has been reported to have a more favorable outcome.[2]

Rossi and colleagues[3] followed 185 CLL subjects from the time of CLL diagnosis to more accurately define the incidence and risk factors for RT. In this cohort, 17 subjects were diagnosed with an RT with an actuarial incidence of 13.6% and 16.2% at 5 and 10 years, respectively, with no further cases diagnosed beyond 82.5 months.[3] Among those subjects who developed RT, the median time to RT was 23 months from the diagnosis of CLL. In univariate analysis, lymph node bulk ($\geq$3 cm), higher numbers of nodal groups involved ($\geq$3), elevated serum levels of lactate dehydrogenase (LDH), diffuse bone marrow involvement, and more advanced Binet stage were all associated with a greater risk for transformation.[3] However, on multivariate analysis, only lymph node bulk remained independently associated with risk of transformation.[3] Other traditional clinical prognostic markers were not found to be associated with greater risk for transformation, including advanced age, poor performance status, Rai stage, cytopenias, lymphocyte count, splenomegaly, percentage bone marrow infiltration, and β_2-microglobulin (β_2M).[3] Importantly for therapeutic purposes, fludarabine exposure was not significantly associated with an increased risk of transformation.[3]

Numerous pathologic and genetic features have been associated with an increased risk of RT. The most potent of these seem to be (1) an unmutated IGVH, (2) the presence of NOTCH1 mutations, and (3) stereotypy of the B-cell receptor. IGVH 4–39 usage has also been associated with an increased risk of RT (particularly when occurring in cases with a NOTCH1 mutation).[4] Other features that have been associated with an increased risk of RT include CD38 expression, ZAP-70 expression, high-risk fluorescence in situ hybridization (FISH) lesions (eg, deletion 17p, deletion 11q), and trisomy 12 (**Box 1**).

Presentation of Richter Transformation: Clinical and Genetic Landscape at Transformation

Recognition of RT can be challenging. In advanced cases, patients can present with a fulminant illness characterized by florid B symptoms (including fatigue, reduced energy, reduction in performance status, significant unintentional weight loss, fevers, night sweats, malaise) and rapidly increasing lymphadenopathy and splenomegaly. In other cases, however, the presentation can be more subtle and even not recognized by less vigilant clinicians without a proactive approach to looking for the condition on lymph node biopsy or PET.[6,7]