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Richter's syndrome: Novel and promising therapeutic alternatives

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A B S T R A C T

Richter's syndrome (RS) is the development of an aggressive lymphoma in patients with a previous or concomitant diagnosis of chronic lymphocytic leukemia (CLL). The incidence rate for RS is ~0.5% per year of observation. In the presence of clinical suspicious of RS, diagnosis of transformation and choice of the site of biopsy may take advantage of ^{18}FDG PET/CT. Molecular lesions of tumor suppression regulators (*TP53*), cell cycle (*CDKN2A*) and cell proliferation (*NOTCH1*, *MYC*) overall account for ~90% of RS and may be responsible for its aggressive clinical phenotype. The prognosis of RS is generally highly unfavorable. However, the pattern of survival is not homogeneous and the clonal relationship between the CLL and the aggressive lymphoma clones is the most important prognostic factor. Rituximab-containing polychemotherapy represents the back-bone for induction treatment in RS. Younger patients who respond to induction therapy should be offered stem cell transplant to prolong survival.

Richter's syndrome

The 2008 World Health Organization (WHO) Classification of Hematopoietic Tumors defines Richter's syndrome as the development of an aggressive lymphoma in patients with a previous or concomitant diagnosis of chronic lymphocytic leukemia (CLL) [1]. The WHO Classification recognizes two distinct pathologic variants of Richter's syndrome: the diffuse large B-cell lymphoma (DLBCL)

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variant, which is the most frequent, and the rare Hodgkin lymphoma (HL) variant [1]. This review will focus on the DLBCL type of transformation.

Morphologically, the DLBCL variant of Richter's syndrome consists of confluent sheets of large neoplastic B lymphocytes resembling either centroblasts or immunoblasts [2–4]. Importantly, CLL cases presenting with numerous proliferation centers and an increased proportion of prolymphocytes and paraimmunoblasts, but lacking clear cut features of DLBCL, should not be diagnosed as Richter's syndrome [5]. Phenotypically, tumor cells invariably express CD20, while CD5 expression is present only in a fraction (~30%) of cases, and CD23 expression is even more rare (~15% of cases) [2]. Based on the analysis of the rearrangement of *IGHV-D-J* genes, most (~80%) of the DLBCL variants of Richter's syndrome are clonally related to the preceding CLL phase, thus representing true transformation [2–4], while a fraction of cases (~20%) harbor distinct *IGHV-D-J* rearrangements compared to the paired CLL, representing *de novo* DLBCL arising in a CLL patient [2–4,6–8].

The incidence rate of Richter's syndrome is ~0.5% per year of observation [9,10]. The median interval between CLL diagnosis and development of Richter's syndrome is ~2 years, indicating that this is a relatively early complication of CLL which may also occur in previously untreated patients [9,10]. The risk of Richter's syndrome development is strongly affected by the somatically acquired genetic lesions harbored by the CLL clone, in particular by the presence of *NOTCH1* mutations, and by the expression of specific molecules facilitating the interaction between the CLL clone and the microenvironment, as exemplified by the expression of the immunoglobulin heavy variable gene (*IGHV*) 4–39 rearranged in a stereotyped fashion (so called “subset 8”). Indeed, CLL harboring *NOTCH1* mutations have a significantly higher cumulative probability of developing Richter's syndrome (45%) compared to CLL without *NOTCH1* mutations (4%) [11–13]. CLL expressing a stereotyped B-cell receptor (BCR) belonging to subset 8 have a very high risk of Richter's syndrome development (17-fold higher than cases without a stereotyped BCR), translating into a cumulative incidence of transformation of nearly 80% at 10 years [3].

CLL treatments do not affect the risk of transformation. Indeed, a systematic assessment of the risk of Richter's syndrome in a randomized trial comparing fludarabine monotherapy to alkylating agent-based regimens as first line therapy for CLL found no impact of initial therapy with fludarabine (compared to chlorambucil or the combination of fludarabine plus chlorambucil) on the risk of transformation to Richter syndrome [9]. Consistent with these results, in the LRF CLL4 trial comparing first line fludarabine vs. chlorambucil vs. fludarabine plus cyclophosphamide, the frequency of Richter's syndrome was not different across the three treatment arms [14].

A fraction of patients with relapsed/refractory CLL who received the Bruton's thyrosine kinase inhibitor ibrutinib developed Richter's syndrome at relapse [15–19]. Many of these events occurred shortly after starting therapy, suggesting that unrecognized Richter's syndrome likely predated the initiation of ibrutinib treatment, rather than a contribution of ibrutinib to clonal evolution. Also, the rate of transformation while on ibrutinib therapy seems to be comparable to that historically reported with other frequently used therapies for high-risk patients [20]. Consistent with the lack of a specific contribution of ibrutinib to Richter's syndrome development, Richter syndrome occurred at similar rates among relapsed CLL randomized to receive ibrutinib or ofatumumab [16].

With the introduction of the anti-CD52 antibody alemtuzumab that causes a profound T-cell depletion, occasional CLL patients have been reported to develop clinically aggressive lymphomas characterized by Epstein–Barr virus (EBV) infection and usually unrelated to the CLL clone [21–24]. These cases of alemtuzumab-associated aggressive lymphomas are clinically and biologically distinct from Richter's syndrome, and should be considered as a novel type of immunodeficiency-related lymphoma developing after T-cell depleting therapies in patients already immunocompromised because of the underlying disease and/or because of previous chemotherapy.

Richter's syndrome diagnosis and course

Richter's syndrome should be suspected in any CLL patient that develops rapid clinical deterioration, fever in the absence of infection, rapid and discordant growth of localized lymph nodes, and sudden and excessive rise in lactate dehydrogenase (LDH) levels. Presence of one or more of these clinical signs and symptoms is only 50–60% specific for Richter's syndrome. In the remaining cases, the