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Highlights : Focus on Indolent Lymphoma

Commentary

Indolent B-Cell Lymphoma : The Current Standard in 2014

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In this issue of the Journal of Clinical and Experimental Hematopathology, five review articles for indolent lymphoma are included. As all of the readers are aware, follicular lymphoma (FL) is one of the most important subtypes of malignant lymphoma. Its initial recognition occurred a long time ago, in the 1960s, and the disease concept was established in the 1970s.[1] However, our basic understanding of FL has recently been changing. FL is mostly a nodal lymphoma, but can also occur in extranodal sites.[2] Takata *et al*. concisely reviewed the pathological perspective of FL, with a special emphasis on intestinal subtypes.[3] Histologically, FL is classified according to the number of large centroblastic cells. Grade 1 FL presents with 0-5 centroblasts per high-power field (hpf), but grade 2 has 6-15/hpf, and grade 3 has more than 15/hpf. Grade 3 is further divided into 3a with centrocytes and 3b with solid sheets of centroblasts. Grade 3B is currently regarded as a distinct entity by molecular genetic analyses, but the independence of grade 3A remains unclear. Histological transformation of FL to large-cell lymphoma occurs in 30-40% of patients, at a rate of approximately 3% per year.

Although there is typical histology of FL, the differential diagnosis of FL from other indolent lymphomas, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), marginal zone lymphomas (MZLs), hairy cell leukemia (HCL), and lymphoplasmacytic lymphoma (LPL), is sometimes problematic.[4] These non-follicular small cell lymphomas usually show infiltration of lymphoma cells that may be diffuse histologically, but sometimes present with intermediate growth with FL, including mantle zone, marginal zone, and interfollicular pattern. They are currently included in the low-grade category owing to several histological similarities, making a differential diagnosis from FL difficult. Sakata *et al*. focused on the pathology of these subtypes of indolent lymphomas other than FL.[5] Immunophenotype and genetic aberrations, as well as morphology, are important for the precise diagnosis. In addition, they introduced a novel category of indolent B-cell lymphoma with *IRF4* translocation, prolymphocytic/paraimmunoblastic lymphoma, from their own experience.[6]

The first recognition of the pathogenic genetic event of FL occurred in the 1970s, namely, the presence of t(14;18) (q32; q21) translocation.[7] Later, an important oncogene for B-cell lymphoma, *BCL2*, was discovered from the breakpoint on chromosome 18.[8] t(14;18) or *BCL2* had long been believed to be the sole genetic event responsible for lymphomagenesis in FL. In recent years, however, many gene aberrations, mostly single point mutations, have been identified in a considerable proportion of FL patients. The current understanding of these molecular events in FL, as well as the implication of the microenvironment, has been summarized by Kishimoto and Nishikori.[9] *MLL2* and *EPHA7* genes are mutated in more than half of FL patients, and more than 10 genes are mutated to varying degrees. More genes are probably affected in FL, and further investigations are warranted to understand the overall pathogenesis of FL.

The prognosis of indolent lymphomas including FL has been good for decades, but it has further improved in recent years after the introduction of rituximab.[10] New approaches for FL, including novel agents, maintenance rituximab, and the use of criteria for estimating tumor burden, have been well reviewed by Izutsu.[11] Watchful waiting is still an option for patients without symptoms and/or low tumor burden. For patients who require treatment, some kind of CD20 antibody should be included for chemoimmunotherapy, although the optimal antibody or combination with chemotherapy has not

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yet been established. In view of the current understanding, it is thus important that other novel molecular-targeted agents are evaluated. In this context, salvage treatments and high-dose chemoradiotherapy can be used to accompany hematopoietic stem cell transplantation (HSCT). The current status of HSCT for FL has been reviewed by Kim.[12] In contrast to other treatment modalities, allogeneic HSCT can be curative for FL, although certain patients suffer transplant-associated mortality. However, in recent years, the toxicity of HSCT has been relieved by reduced-intensity conditioning regimens. The position of HSCT has also been shifted by the introduction of rituximab and further molecular-targeted agents.

I believe that the readers of the Journal of Clinical and Experimental Hematopathology can readily understand the latest status of indolent lymphoma via these five review articles. Hopefully, readers will obtain new insights into future directions in the management of patients with indolent lymphoma who await novel management by expert hematologists/pathologists.

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