

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Aggressive B-Cell Lymphoma: The Double-Hit and Double-Expressor Phenotypes

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H&O What are some recent developments in the understanding of genetics in aggressive B-cell lymphoma?

SS There are between 60 and 80 different types of non-Hodgkin lymphoma. Historically, lymphomas have been defined by their histologic or morphologic features. We have recently learned, however, that the biology is also important in several ways: it can provide prognostic information, it might identify newer types of lymphoma, and it could indicate settings in which treatment may need to be altered. Disease biology might predict response to treatment, and it has the potential to impact treatment decision-making.

The starting point in a discussion about genetics in aggressive B-cell lymphoma is the observation that some patients can be cured and others cannot. Studies have investigated the biologic underpinnings for these different outcomes. A pioneering genetic evaluation of diffuse large B-cell lymphoma (DLBCL), published by Alizadeh and colleagues in 2000, showed 2 subtypes: germinal center and non-germinal center (also known as *activated*). The name *germinal-center DLBCL* was chosen because the gene expression of this profile more closely fits with the normal germinal center–derived B cell. In the subtype non-germinal center DLBCL, or activated B-cell lymphoma, the gene expression profiling more closely fits a normal activated B cell. This distinction is important because better outcomes are seen in patients with the germinal-center subtype than with the non-germinal-center subtype. We therefore now have a “cell-of-origin” model showing that there are at least 2 genetic biologic

types of DLBCL that might explain prognosis and could perhaps be targeted differently. This insight from 15 years ago has led to recent trials that are specifically powered to test new treatments in one genetic subtype vs the other. We are hopefully very close to understanding whether these 2 subtypes of DLBCL should be treated differently. There are several other genetic models that may also be important, focusing on inflammation and host immune response, but the “cell-of-origin” model has been the main concept tested in clinical trials.

H&O What does the term *double-hit lymphoma* refer to?

SS The t(8;14) translocation, in which *MYC* is rearranged, is classically associated with Burkitt lymphoma, a very aggressive and fast-growing lymphoma. Approximately 10 years ago, it became clear that the t(8;14) translocation was also seen in DLBCL, as well as in another type of lymphoma that shares morphologic features of both DLBCL and Burkitt lymphoma.

The t(14;18) translocation, which involves the rearrangement of *BCL2*, is also important in lymphoma and leads to a drug-resistant phenotype with increased cancer cell survival. The presence of both the *MYC* and *BCL2* rearrangements is known as *double-hit lymphoma*. This phenotype is very proliferative and drug-resistant, and it is associated with a poor prognosis.

The dual rearrangement of *MYC* and *BCL2* occurs in approximately 5% to 7% of patients with DLBCL and can also occur in lymphomas with morphologic features intermediate between DLBCL and Burkitt lymphoma.

This “intermediate” lymphoma has recently been reclassified as “high-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements.”

Another variant of double-hit lymphoma is co-rearrangement of *MYC* and the *BCL6* gene. Rarely, all 3 genes—*BCL2*, *MYC*, and *BCL6*—are simultaneously rearranged in a phenotype termed *triple-hit lymphoma*. Both double-hit and triple-hit lymphomas have a poor prognosis with standard treatment.

H&O What is the clinical significance of double-hit lymphoma?

SS The clinical significance of double-hit lymphoma is that standard treatment, such as rituximab (Rituxan, Genentech/Biogen) plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), is subopti-

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mal. Few patients with double-hit lymphoma are cured with this approach. Currently, the best treatment for double-hit lymphoma is unknown. There are retrospective reviews suggesting that a more intensive therapy, such as etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab (EPOCH-R), may be better than standard treatment. Prospective trials are underway.

An additional challenge is that we do not know the clinical significance of genes that are amplified or duplicated (but not rearranged). The most common example is the presence of 2 or 3 extra copies of *MYC*. Currently, that profile is not considered double-hit lymphoma, and there are no clear treatment guidelines.

H&O What does the term *double-expressor* refer to?

SS Immunohistochemical staining to identify protein expression of *MYC* also showed that there are lymphomas in which *MYC* and *BCL2* genes are overexpressed at a

protein level, without the genetic rearrangements. Dual-expressor protein, or double protein, refers to immunohistochemical detection of *MYC* and *BCL2* overexpression. This profile was referred to as the “double-expressor” phenotype in DLBCL in the revised World Health Organization (WHO) classification of lymphoid neoplasms, which was published in 2016 in *Blood*.

The cut points to define overexpression vary from study to study. The WHO classification defines overexpression as greater than 40% *MYC*-expressing cells and greater than 50% *BCL2*-expressing cells. As shown in a study by Hu and colleagues, patients with double-expressor DLBCL have worse outcomes than patients in whom these proteins are not overexpressed; in general, only one-third of patients have long-term disease control with R-CHOP.

H&O Approximately how many patients fit into these categories?

SS Double-hit lymphoma is relatively uncommon, occurring in approximately 5% to 7% of patients with DLBCL. Dual-expressor lymphomas may be present in as many as one-third of patients with DLBCL.

H&O Are the double-hit and double-expressor phenotypes related?

SS Double-hit lymphoma and double-expressor lymphoma are probably related, but are different categories. Patients who have the double-hit rearrangement usually have protein overexpression, and therefore have the double-expressor phenotype. However, the converse is not always true: dual-expressor protein overexpression is not always associated with an underlying double-hit rearrangement.

Complicating the picture is that most double-hit lymphomas occur in the setting of a germinal-center DLBCL, whereas most double-expressor lymphomas occur in non-germinal-center DLBCL.

H&O How are these genetic profiles detected?

SS The double-hit lymphomas can be detected with fluorescence in situ hybridization (FISH) or standard cytogenetic analysis. The double-expressor lymphomas are diagnosed by immunohistochemistry.

The most challenging profile to detect in routine practice is “cell of origin.” The gold standard for identifying germinal-center DLBCL vs non-germinal-center DLBCL was first defined as gene-expression profiling patterns in frozen tumor material. However, gene-expression profiling is not routinely available nor is it considered

a standard test. The most common approach is immunohistochemistry using different algorithms, such as the Hans algorithm, to approximate whether the lymphoma is germinal-center DLBCL or non-germinal-center DLBCL. Compared with the gold standard of gene expression profiling in frozen material, there is an error rate of approximately 20% with immunohistochemical algorithms. A new parsimonious digital gene-expression assay (Lymph2Cx; NanoString), which is being tested in clinical trials but is also available commercially, looks at 20 genes to help determine cell of origin.

H&O How did the WHO revise its classification of lymphomas?

SS The importance of these genetic drivers (*MYC* and *BCL2*) led the WHO to recently revise the classification of aggressive B-cell lymphomas. Categorization now involves both morphology and genetics. A new category is “high-grade B-cell lymphoma (HGBL), with *MYC* and *BCL2* and/or *BCL6* rearrangements,” which encompasses double-hit lymphoma. This new category is based not only on morphology but on the presence of *MYC* and *BCL6* rearrangements, and includes any histology that harbors these rearrangements.

The double-expresser phenotype was not given a unique category, but was recognized by the WHO as a poor prognostic sign within DLBCL.

H&O How can knowledge of these phenotypes improve clinical care?

SS Most of these observations, whether it is cell-of-origin, double-hit lymphoma, or double-expresser lymphoma, currently inform prognosis. The next step for the management of these patients is to understand how they can become predictive factors and guide the development of targeted therapies. Is there any therapy that will work preferentially in some of these poor-prognosis subgroups? In both the frontline and relapsed/refractory settings, the only way to move forward is to design trials that are powered to test specific subsets. Patients with DLBCL or aggressive B-cell lymphoma should seek out clinical trials that specifically evaluate new treatments for these subsets. Trials for these patients might differ from standard trials in that they will likely incorporate a central review using pathology, adequate biopsy, or an assay such as a digital gene-expression test to determine each patient’s subset. The issue of having an adequate biopsy is an important one. Many patients that we see for second opinions come in with fine needle aspirates or tiny core biopsies that do not permit determination of these prognostic features. It is very important to have

enough tissue in biopsies to provide optimal clinical care and to move this field forward.

H&O Are there any promising treatments for relapsed/refractory disease?

SS When patients with aggressive B-cell lymphomas relapse or become refractory to therapy, standard options are limited. For patients unable to undergo transplant, or for those who relapse after a stem cell transplant, the median survival is approximately 6 months. Despite the many trials that have tried to improve upon this dismal statistic, there are no breakthroughs at this time. Chimeric antigen receptor (CAR) T-cell therapy is exciting. This treatment is still in the early phases of research and associated with toxicity, but it is promising for patients with aggressive B-cell lymphomas that do not respond to other therapies. There are also a number of new biologic and targeted agents that are promising, and finding which patients may respond to a particular treatment is a high priority.

Disclosure

Dr Smith has performed consulting for Adaptive, AbbVie, TG Therapeutics, Pharmacyclics, Portola, Forty Seven, Celgene, Gilead, and Genentech/Roche.

Suggested Readings

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