ADVANCES IN LLM

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Evolving Management of Patients With Double-Hit Lymphoma

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

AL Double-hit lymphoma is an aggressive B-cell lymphoma with *MYC* translocation and a *BCL2* and/or *BCL6* translocation. The diagnosis requires a rearrangement of the genes, rather than extra copies.

H&O What are the clinical features of double-hit lymphoma?

AL Most patients tend to present with aggressive, symptomatic disease with extranodal sites, a high International Prognostic Index score, and high levels of lactate dehydrogenase. Recently though, we have seen more reports of double-hit lymphoma in patients with lower-stage disease that appears less clinically aggressive. At my institution and many others, pathologists routinely perform fluorescence in situ hybridization (FISH) to check for a *MYC* rearrangement in all patients with diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma. From a pathologic perspective, double-hit lymphoma can appear identical to standard DLBCL. A small subgroup of patients have disease with a more aggressive histologic appearance, similar to Burkitt lymphoma. These patients typically have *BCL2* translocations or overexpression. If a pathologist performs a workup for Burkitt lymphoma in these patients, he or she will find that the immunophenotypic characteristics do not support this diagnosis and will therefore perform FISH to evaluate for double-hit or triple-hit lymphoma.

H&O Are there any recent insights into the biology of double-hit lymphoma?

AL Most cases of double-hit lymphoma fall into the germinal center B-cell (GCB) subtype in the cell-of-origin classification. Investigators such as Drs Margaret Shipp and Louis Staudt have moved beyond the cell of origin to identify more refined subgroups of aggressive B-cell lymphoma using comprehensive assessments of gene mutations and copy number changes. Double-hit lymphoma falls into the EZB group in Staudt's LymphGen classification and cluster 3 in Shipp's DLBCL clusters.

Ongoing research is further evaluating additional factors contributing to the poor prognosis of these patients. A large analysis from the Lunenburg Lymphoma Biomarker Consortium found that patients in whom *MYC* is partnered with an immunoglobulin gene, most commonly the heavy-chain gene, appear to have the most aggressive course and worse outcome compared with other gene partners. Most pathologists assess for *MYC* rearrangements using a break-apart probe, where the partner gene is not identified. In the future, however, more centers may evaluate for the partner gene, particularly if data confirm that immunoglobulin partner genes drive poor outcomes.

The prognostic implication of a *BCL6* rearrangement

is controversial. Recently, there has been some question as to whether patients with *MYC* and *BCL6* rearrangements have the same poor outcomes with standard rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) as patients with double-hit lymphoma with *MYC* and *BCL2* rearrangements. In the study by the Lunenburg Consortium, prognosis appeared to be similar in both groups of patients, although the numbers were small.

H&O How does double-hit lymphoma differ from other lymphomas?

AL Outcomes with R-CHOP are much worse in patients with double-hit lymphoma vs non–double-hit DLBCL. Researchers have studied the use of more aggressive chemotherapy regimens, such as those used in Burkitt lymphoma, including a modified Magrath regimen; fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD); and dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH). In retrospective series, these treatments appear to improve progression-free survival, but not necessarily overall survival. Only one prospective phase 2 study has examined the treatment of *MYC*-rearranged aggressive lymphomas. This multicenter study, performed by Dr Kieron Dunleavy and colleagues, evaluated treatment with dose-adjusted R-EPOCH. The trial enrolled patients with both single-hit and double-hit lymphomas. At 48 months, the rate of event-free survival among the entire population was 71%. Treatment with R-EPOCH led to better outcomes than expected, which might be attributable to the patient population. Patients with double-hit lymphoma are often too sick to participate in clinical trials. Enrolling patients on studies takes time and can sometimes be difficult in hospitalized populations. When patients need immediate therapy, we will often initiate treatment with R-CHOP. We are aware that these patients may in fact have double-hit lymphoma, and that treatment will need to transition to dose-adjusted R-EPOCH. It is unclear whether the population in the prospective study reflects the typical group of patients we treat with double-hit lymphoma. Double-hit lymphoma can also arise in the context of an underlying follicular lymphoma that transforms after previous treatment. Outcomes are much worse among patients who were previously treated with cytotoxic chemotherapy.

Some patients with double-hit lymphoma have extensive bone marrow disease, sometimes with lymphoma circulating in the blood. This scenario is particularly challenging to treat, and these patients have a very high risk of central nervous system (CNS) involvement. Intrathecal chemotherapy does not adequately penetrate the brain parenchyma. Administration of systemic methotrexate with dose-adjusted R-EPOCH is difficult. These patients represent an unmet need.

H&O Does the evaluation process differ for patients with double-hit lymphoma?

AL Clinicians may evaluate the cerebral spinal fluid at baseline in high-risk patients, even in the absence of symptoms. Until recently, most academic centers administered CNS prophylaxis to patients with high-risk DLBCL. Recent data, however, suggest that this strategy is not effective in these patients. The value of CNS prophylaxis in double-hit lymphoma is unclear and controversial.

> CAR T-cell therapy provides a glimmer of hope for patients with primary refractory or relapsed disease.

H&O What factors guide treatment selection in double-hit lymphoma?

AL Currently, patients with double-hit lymphoma receive dose-adjusted R-EPOCH. R-CHOP is not adequate, as outcomes are inferior to those seen in DLBCL. In the prospective study, the rate of event-free survival was 71%. However, the rate in clinical practice is somewhat lower, likely given the selection bias toward enrollment of healthier patients in phase 2 studies. For young patients with double-hit lymphoma, particularly those with extensive disease in the bone marrow, options include the modified Magrath regimen or hyper-CVAD. These treatments include CNS-directed therapies. Pediatricians use these very aggressive regimens in patients with Burkitt lymphoma and DLBCL. Prospective clinical trials are needed.

H&O Are there any promising novel treatments?

AL Chimeric antigen receptor (CAR) T-cell therapy provides a glimmer of hope for patients with primary refractory or relapsed disease. Although the reported number of patients is small, outcomes appear to be encouraging in double-hit lymphoma. By targeting

CD19 on the lymphoma cell surface, CAR T-cell therapy has a completely different mechanism of action and may be effective in patients whose disease is resistant to standard chemotherapy. CAR T cells may be used earlier in high-risk patients.

In addition, a number of novel drugs that target cell-surface markers, such as tafasitamab-cxix (Monjuvi, Morphosys/Incyte), loncastuximab tesirine-lpyl (Zynlonta, ADC Therapeutics), and polatuzumab vedotin-piiq (Polivy, Genentech), may be effective in double-hit lymphoma. More data are needed.

H&O What are the unmet needs in double-hit lymphoma?

AL Traditionally, outcomes in patients with double-hit lymphoma have been poor, particularly for those with concurrent CNS disease. Many patients are resistant to initial therapy and develop rapidly progressive, chemotherapy-refractory disease. Treatment with rituximab, ifosfamide, carboplatin, and etoposide (RICE) or standard salvage regimens is rarely effective, and few patients make it to stem cell transplant. Thankfully, we now have CAR T-cell therapy and other novel approaches. One of the first patients I enrolled on a CAR T-cell trial with double-hit lymphoma remains in a durable remission 5 years after treatment.

Incorporating these novel agents and approaches earlier in the treatment course will likely lead to better responses. When these patients become sick, they are often highly symptomatic and tolerate any therapy poorly owing to their poor performance status and the organ toxicity caused by the disease or cytotoxic chemotherapy.

H&O Are there any other areas of research in double-hit lymphoma?

AL Scientists are trying to better understand the biology of double-hit lymphoma and disease heterogeneity to identify potential therapeutic targets. In lymphoma, we have amazing laboratory-based scientists who are dedicated to the field. Many advances have already been made, and I am hopeful that management of these patients will continue to improve.

H&O Do you have any other observations regarding the management of patients with double-hit lymphoma?

AL From a clinical perspective, it is important to recognize patients with aggressive disease early. In the patients with localized disease that is clinically less aggressive, we need studies to determine optimal management. It is not known whether they need more aggressive treatment or if they may do well with R-CHOP. Fewer than 10% of patients with aggressive lymphoma have double-hit lymphoma. It is critical for scientists and clinicians to work together to study this disease from both biologic and therapeutic perspectives.

Disclosure

Dr LaCasce has no relevant conflicts of interest to report.

Suggested Readings

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