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EDITORIAL

Twenty years later: has cell of origin testing in diffuse large B cell lymphoma run its course?

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Diffuse large B cell lymphoma (DLBCL) is the most common type of adult non-Hodgkin lymphoma, typically has an aggressive clinical course, and is generally treated with multiagent therapy. In the immunochemotherapy era, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) is the therapeutic standard of care for newly diagnosed DLBCLs and has produced an overall survival (OS) of approximately 60% [1].

A variety of clinical prognostic factors have been identified for DLBCL, including the International Prognostic Index, maximum tumor diameter (as estimate of tumor bulk), vitamin D level, serum free light chain levels, peripheral blood absolute lymphocyte/monocyte ratio, and concordant versus discordant bone marrow involvement, among others [2–7]. Multiple tumor-associated biomarkers also have been reported to have prognostic significance in DLBCL, such as CD5 expression, CD30 expression, dual expression of MYC and BCL2 proteins, *MYC* gene rearrangements, and *TP53* mutations, among others [8–12]. Most of these have had conflicting results published in subsequent studies and have shown varying degrees of prognostic robustness.

Over the past 20 years, cell of origin (COO) testing has received considerable attention as a prognostic marker in DLBCL. In 2000, Alizadeh and colleagues used cDNA microarrays on fresh frozen tissue from de novo DLBCLs and identified two main molecularly distinct types of DLBCL: one similar to the gene expression pattern by normal germinal center B cells (germinal center B cell-like (GCB)) and the other resembling those of activated peripheral blood B cells (activated B cell-like (ABC)) [13]. This study also demonstrated better OS among patients with the GCB-like DLBCL than for those with the ABC-like DLBCL. The study by Rosenwald and associates corroborated the latter clinical findings [14], which cemented COO testing as a prognostic indicator for DLBCLs.

Since gene expression profiling (GEP) required using fresh or frozen tissue samples at that time, an impractical technology for everyday clinical use, an immunohistochemical (IHC) staining method performed on formalin-fixed paraffin-embedded (FFPE) tissue sections was sought that could serve as an effective surrogate for the former technique. Several IHC methods were published, but the one that has stood the test of time and has become the favored current modality was reported by Hans et al. [15]. This study used antibodies directed against CD10, BCL6, and IRF4 (MUM1) on FFPE tissue microarrays from de novo DLBCLs, most of which had been part of the earlier GEP studies [13, 14]. They developed an algorithm based on the staining patterns that divided the DLBCLs into two subgroups, GCB and non-GCB, which had similar 5-year OS as the GCB-like and ABC-like groups from the cDNA microarray studies.

The use of Hans' algorithm or of a more recent GEP technique applicable to FFPE tissues [16] to define COO of DLBCLs for clinical prognosis and possibly for therapeutic guidance is now required at the time of initial diagnosis by the current World Health Organization (WHO) classification of lymphoid neoplasms [17]. Recent pathologic studies, however, have called into question the prognostic value of COO determination by GEP or by IHC in DLBCL as compared to double expression of MYC and BCL2 proteins and to the presence of *MYC* gene rearrangement [18, 19].

COO testing has also become standard to stratify DLBCLs into prognostic subgroups for clinical trials seeking novel agents to add to R-CHOP in an attempt to improve clinical outcome, particularly for patients with the ABC-like/non-GCB subtype. Unfortunately, results of recent clinical trials have failed to show COO determination is a predictive biomarker for making specific treatment decisions for patients with DLBCL. The PYRAMID and REMoDL-B trials found no significant benefit to adding bortezomib to R-CHOP for

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patients with the ABC-like/non-GCB subtype of DLBCL [20, 21]. Nor did the PHOENIX trial indicate an advantage to adding ibrutinib to R-CHOP for patients with the ABC-like DLBCL subtype [22]. Most recently, the ROBUST trial showed adding lenalidomide to R-CHOP provided no significant improvement in the primary progression-free survival endpoint for patients with ABC-like DLBCL (presented by Dr. Umberto Vitolo at the International Conference on Malignant Lymphoma, June 18–22, 2019, Lugano, Switzerland).

Three recent studies that focused on the mutational landscape of DLBCLs have identified high-risk mutational profiles among DLBCLs, some of which appear COO-independent [23–25]. Their findings provide a rationale for targeted therapies, such as one that used clinical data in concert with DNA and gene expression analysis to identify a high-risk subgroup of patients with non-GCB DLBCLs who benefit from the addition of lenalidomide to R-CHOP [26].

Now, after 20 years, it is apparent that COO testing for DLBCLs has lost its luster but is not yet obsolete despite its questionable prognostic value and lack of predictive utility.

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