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Biomarkers in diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is a clinically heterogeneous disease, affecting patients of all ages and presenting as limited or advanced disease in essentially any nodal or extranodal site in the body. Gene-expression profiling defined 3 molecular subtypes of DLBCL, termed germinal center B-cell-like (GCB), activated B-cell-like (ABC), and primary mediastinal B-cell lymphoma (PMBL). GCB-like DLBCL has a more favorable prognosis than ABC-like regardless of therapy with CHOP or R-CHOP.[1,2] Additional genome-wide copy number analysis coupled with gene-expression profiling provide evident that the DLBCL subtypes are distinct diseases using different oncogenic pathways with implications for future treatments.[3] Calculation of a survival score from a six-gene model is also predictive in the R-CHOP era, and this model has been successfully applied to routine formalin-fixed paraffin embedded tissue.[4] To date, it has not been possible to reliably replicate the cell of origin with routine immunohistochemistry, in part due to lack of reproducibility with markers such as bcl-6.[5,6] Recent data suggest that a 9 microRNA signature can differentiate the two subtypes of DLBCL and that some of the microRNAs in this signature correlate with clinical outcome.[7] Additional subtypes of DLBCL have been identified, one of which has been specifically related to the B-cell receptor signaling pathway and its inhibition.[8,9] Most recently, attention has turned to the microenvironment because two new signatures, termed "stromal-1" and "stromal-2" predicted survival in R-CHOP treated patients.[2] The prognostically favorable stromal-1 signature reflected extracellular-matrix deposition and histiocytic infiltration whereas the unfavorable stromal-2 signature reflected tumor blood-vessel density. Evaluation of response by interim positron emission tomography (PET) imaging has been associated with high predictive accuracy in DLBCL treated with chemotherapy.[10,11] With the use of R-CHOP and evaluation of PET imaging in multiple settings, the interpretation and predictive value has come into question.[12-14] In particular, false positive readings have been associated with intense chemotherapy and rituximab combinations, use of growth factors, and readings of minimal residual uptake by radiologists or equivocal interpretation by clinicians. Recently, lack of agreement among expert radiologists has been presented.[15] Determination of the best timing of interim PET imaging, use of standardized reading criteria (qualitative and

quantitative), training and consistent interpretation by radiologists, and evaluation according to therapeutic intervention are all necessary to using PET as a valid biomarker. With increased understanding of the heterogeneity of DLBCL, the future challenge is to incorporate biomarker evaluation in the context of clinical trials toward the development of targeted, biologically-based therapies.

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