# Follicular lymphoma grade 3B: low grade, high grade or should we skip the grade?

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Grade 3B follicular lymphoma (G3BFL) is an infrequent subtype of follicular lymphoma (FL) accounting for approximately 5-10% of all FL cases.[1] G3BFL has been historically defined visually by the presence of solid sheets of centroblasts with at least a partial follicular pattern identified by morphology or immunohistochemistry, in contrast to diffuse large B-cell lymphoma (DLBCL), which has lost its follicular architecture, and grade 3A FL (G3AFL) which has admixed centrocytes and centroblasts.[2] G3BFL is comprised of nearly 50% composite forms with concurrently identified lower-grade FL or DLBCL in biopsy specimens.[2] Due to questionable reproducibility in grading and the overall rarity of cases, G3BFL cases have often been excluded from both FL and DLCBL clinical trials. While controversial, the subdivision between G3AFL and G3BFL has been proposed to have biological and clinical relevance, with G3BFL believed to behave more similarly to DLBCL than to indolent FL.[1,3] Current clinical approaches are derived largely from historical perspectives and have focused on treatment with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) plus rituximab, without good prospective evidence. Therefore, precise prognostication and optimal therapeutic strategies for G3BFL remain undetermined.

Barraclough and colleagues have now conducted the largest international analysis of G3BFL in the rituximab era, evaluating the outcomes of 157 patients with G3BFL at a median follow-up of 5 years.[4] They included cases of composite G3A/3BFL, pure G3BFL, and G3BFL/DLBCL along with large G3AFL and DLBCL comparator groups. In line with current treatment paradigms, patients with G3BFL received rituximab or obinutuzumab combined with CHOP or CHOP-like chemotherapy. Notably, 37% of patients also received maintenance anti-CD20 therapy (with rituximab or obinutuzumab). G3AFL cases were treated with either rituximab- or obinutuzumab-CHOP-like chemotherapy (74%) or bendamustine plus rituximab (26%) with rituximab or obinutuzumab maintenance therapy in 68% of cases. DLBCL cases received rituximab- or obinutuzumab-CHOP-like chemotherapy. In this analysis, both the 5-year progression-free survival and 5-year overall survival of patients with G3BFL were found to be equivalent to those of patients with G3AFL and were statistically significantly longer than the 5-year progression-free survival and 5-year overall survival of patients with DLBCL.

Prognostic factors in G3BFL identified in this study included CD10 negativity and stage III/IV (inferior progression-free survival), as well as elevated lactate dehydrogenase, poor performance status, and age >60 years old (inferior overall survival). The Follicular Lymphoma International Prognostic Index[5] showed poor discrimination of risk groups in G3BFL, while the Revised International Prognostic Index (R-IPI)[6] showed a statistically significant difference between risk groups with low, intermediate, and high risk 5-year overall survival rates of 100%, 85%, and 64%, respectively ($P$<0.001). The performance of these scales in G3BFL has not been previously evaluated and the findings presented here are important. A key caveat (and potential criticism) of this study is the inclusion of a significantly high risk DLBCL cohort used as a comparison group. As compared to either the G3AFL or G3BFL subgroup, DLBCL cases were more likely to be older, with worse performance status, elevated lactate dehydrogenase, more frequent extranodal involvement, and higher IPI scores. DLBCL cases had an atypically poor 5-year progression-free survival (54%), and a high proportion of high-risk R-IPI scores (51%). The disparate outcomes observed between G3BFL and DLBCL are likely influenced at least in part by these differences, which may have a biological origin, however comparisons between risk subgroups in each disease cohort would be more informative in evaluating potential differences. A major challenge in studying G3BFL is the poor reproducibility of grading, influenced by sampling (as transformation is not a uniform event), definition and morphological identification of centroblasts, and methods of enumeration. Central pathology review was not conducted in this analysis. This issue is relevant given that grading discrepancies have

been reported in up to 40-60% of FL cases.[2,3,7,8] CD10 negativity in G3BFL was associated with inferior progression-free survival, a feature that has been previously suggested to indicate a closer relationship to DLBCL rather than to low-grade FL.[2] Inclusion of MUM1 and BCL6 immunohistochemical analysis as well as fluorescence *in situ* hybridization analysis for BCL2, BCL6, and MYC would strengthen the authors' findings as important discrepancies in immunophenotype have been previously observed between low grade FL, G3A/3B FL, and DLBCL.[1,9,10] When treated with rituximab-CHOP-like chemotherapy, outcomes appear to be similar between patients with G3BFL and G3AFL, with less similarity between those with G3BFL and DLBCL. Advances in genetic characterization and revisions in classification systems may influence our understanding and identification of G3BFL in the future, and further prospective studies that include this rare subtype are needed. The R-IPI score appears to perform well in identifying patients with G3BFL at higher risk of poor outcomes when treated with chemoimmunotherapy and may be a useful tool when considering treatment approaches for G3BFL. CD10 negativity also appears to identify higher risk cases. It seems reasonable to consider including patients with G3BFL with low- or intermediate-risk R-IPI scores in FL studies while excluding them from DLBCL studies, provided that they received rituximab-CHOP-like chemoimmunotherapy in the frontline setting.

**Disclosures**

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**Contributions**

*EM was the primary author with a contribution from JPL.*

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