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EDITORIAL

Something Old, Something Few, Something Subjective, Something D  j   Vu

IN THE absence of significant differences in survival with approaches ranging from observation to stem cell transplantation, there is a lack of consensus on the optimal primary treatment of advanced stage follicular lymphoma. In this issue of the *Journal of Clinical Oncology*, Peterson et al,¹ from the Cancer and Leukemia Group B (CALGB), report no difference in complete response rate, time to failure, or overall survival with single-agent cyclophosphamide or CHOP-B (cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin) combination chemotherapy in advanced stage follicular lymphoma. However, in an unplanned subgroup analysis of histologic subtype, time to failure and event-free survival were significantly longer among the 23 patients with follicular mixed (FM) lymphoma who were treated with CHOP-B compared with the 23 FM patients who were treated with cyclophosphamide. At 10 years, 11 FM patients receiving CHOP-B were alive and failure free compared with two FM patients treated with cyclophosphamide. The patient numbers are small, but so are the *P* values. How should these data be interpreted?

Strictly interpreted, the CALGB trial is an important *negative* study, demonstrating no advantage to initial aggressive therapy in low-grade follicular lymphoma. This is not what will be remembered, however, and is not what the authors have highlighted in their abstract. Rather, the authors generate the hypothesis that CHOP-B may provide better outcome in FM patients, on the basis of an unplanned subgroup analysis. The data renew the 1980s controversy regarding the distinction between follicular small cleaved (FSC) and FM subtypes. The report of prolonged initial remission in 19 patients with FM lymphoma treated with C-MOPP (cyclophosphamide, vincristine, procarbazine, prednisone) chemotherapy was followed by the report of a randomized trial in 52 FM lymphoma patients failing to confirm prolonged disease-free survival with the COPP (cyclophosphamide, vincristine, procarbazine, prednisone) regimen.^{2,3} Similar to the current report, these studies contained too few patients for reliable conclusions; in addition, conventional chemotherapy was not used. These studies and the current report also raised issues of dose intensity. The current CALGB study is notable for unconventional dose modification and significantly greater dose reductions in the cyclophosphamide arm. In a much larger experience with CHOP chemotherapy, from the Southwest

Oncology Group, a continuous pattern of relapse was observed in both FSC and FM subgroups.⁴

Of course, the prognostic value of histologic grade is meaningless unless the diagnosis is reproducible. As evidenced by a revision of the referral diagnosis of FM lymphoma in more than half of the cases in the current trial reported by Peterson et al,¹ the distinction between small cleaved and mixed categories is beyond the abilities of most community pathologists. The distinction is a problem for the experts, too. In a collaborative study undertaken in 1985 by the cooperative groups, methods of estimation and cell counting were compared among seven expert hematopathologists. All seven pathologists agreed only once (2.5%) with a diagnosis of FM lymphoma, leading to the following statement: "These data suggest that the potential for faulty choice of therapy is present in a high percentage of cases."⁵ To further complicate the issue, an adequate biopsy may demonstrate differences in pattern (follicular and diffuse) as well as cytology, and both pattern and cytology may vary in different microscopic areas of a single biopsy.

How does the new World Health Organization classification of hematopoietic and lymphoid tumors handle the controversy of morphologic subclassification of follicular lymphoma? In the new classification, follicular lymphomas are graded as 1, 2, or 3 according to a definition based on the number of centroblasts (large transformed cells) per high-power field.⁶ These grades correspond to FSC (grade 1), FM (grade 2), and follicular large (grade 3) cell categories in the Working Formulation nomenclature. Using these grading criteria and a consensus diagnosis among expert pathologists in a cohort of 309 consecutive cases in the Non-Hodgkin's Lymphoma Classification Project, no differences in survival were observed between follicular grade 1 and 2, regardless of whether doxorubicin-containing chemotherapy was used.⁷ However, patients with grade 3 follicular lymphoma clearly derived a survival benefit from doxorubicin-containing therapy and were the only group with the suggestion of a plateau on the failure-free survival curve. These data are in agreement with previous reports in follicular large cell lymphoma.^{8,9} There *is* something important about the proportion of large cells in follicular lymphoma, but it seems to be reliably predictive only when large cells predominate.

Clinicians know that a single parameter such as cytologic subtype is never considered in isolation for an individual patient with follicular lymphoma. Clinical presentation is important and should be factored together with the pathologic features. Prognostic schema have been put forth for follicular lymphoma, including the international index and the recent follicular lymphoma international prognostic project index. In the latter, three risk groups with distinct survival patterns are identified on the basis of age, stage, sex, number of nodal sites, marrow involvement, lactate dehydrogenase (LDH), hemoglobin, and lymphocyte count.¹⁰ Meanwhile, outcome prediction based on biologic parameters is in progress. Follicular lymphomas regularly display cytogenetic abnormalities beyond the t(14;18) translocation.¹¹ Analyses of cytogenetic and molecular features are leading to identification of subsets of follicular lymphoma and are providing insights into clonal evolution and transformation. Molecular profiling of larger patient cohorts with follicular lymphomas is under way.

Should all patients with FM lymphoma receive doxorubicin-containing chemotherapy on the basis of this CALGB study? No, but we should consider cytologic subtype and architectural

pattern in the spectrum of histopathology (< 50 large cells/high power field (hpf) versus > 150 large cells/hpf) of follicular lymphoma together with the spectrum of clinical features at presentation (IIIA—low tumor burden and normal LDH—versus IVB—high tumor burden and elevated LDH). As with any spectrum, it is easier to identify patients at either end, whereas in the middle or with “mixed” features, the distinctions are far less apparent. A resurrection of the debates of the 1980s is not warranted because histologic grading will always be subjective and poorly reproducible. Of note, more than half of the FM cases in the CALGB central review were called FSC by the referring pathologists.

It is time to move forward. This is the era of molecular diagnosis and outcome prediction. Now, more than ever, it is important for both patients *and* their fresh tissues to enter clinical trials. We need something bold, something adequately powered, something objective. . . something new.

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