To the editor:

BCL-6 and rituximab in diffuse large B-cell lymphoma: where are we?

We read with interest the paper by Winter et al.1 in which they report the impact of BCL-6 protein expression on outcome in diffuse large B-cell lymphoma (DLBCL) patients treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with rituximab (R-CHOP) or without. These findings provide potentially important insights into DLBCL treatment and rituximab action. Perhaps most revealing is the apparent limitation of rituximab benefit to BCL-6−/− DLBCL. This finding can mostly account for the 18% to 20% improvement in failure-free survival (FFS) observed in randomized studies of CHOP with or without rituximab when one considers that approximately a quarter of DLBCLs are BCL-6−/− and rituximab improved FFS by 67% at 2 years in the present study.2-4

Our interpretation of these results differs from the accompanying Inside Blood commentary that concludes that the benefit of rituximab in BCL-6−/− cases was based on “only” 8 patients and that the 82% FFS of R-CHOP at 2 years in BCL-6+ DLBCL will be difficult to improve upon. These conclusions are based only on responding patients. When one considers all patients and excludes the effect of maintenance, which confounds FFS, the effect of rituximab in BCL-6− cases is based on 21 patients. Furthermore, the FFS of R-CHOP in BCL-6− cases is approximately 40% at 3 years, a more mature time point given the 3.4-year median follow-up.

These results raise provocative biologic questions. We found that, when examined by microarray, BCL-6 mRNA varies considerably among previously defined DLBCL subgroups (Figure 1).5,6 If one arbitrarily divides DLBCL in 2 groups based on the median BCL-6 mRNA expression, most (77%) germinal center B cell–like (GCB) DLBCLs are BCL-6−. However, BCL-6+ cases are also found among activated B cell–like (ABC; 28%), primary mediastinal B-cell lymphoma (PMBL; 38%), and unclassified (47%) DLBCLs. Conversely, BCL-6− cases are most frequent in ABC but also present in other DLBCL subgroups. These considerations suggest that the BCL-6− and BCL-6+ groups in the Winter et al study1 were molecularly heterogeneous and argue for the inclusion of gene expression profiling in the context of DLBCL clinical trials.

The mechanism(s) by which rituximab exerts its effect in DLBCL is unclear. As Winter et al.1 indicate, ABC DLBCL depends on the constitutive activity of the IkB kinase and the NF-κB pathway for survival and may be modulated by rituximab.7 In vitro, however, rituximab treatment does not alter the IkB kinase activity of the OCI-Ly3 ABC cell line (L.M.G., unpublished observation, November 2006), unlike reports in Burkitt lines.8 Nevertheless, it remains possible that rituximab modulates the NF-κB pathway in vivo and directly induces apoptosis and/or sensitizes such tumors to CHOP. In this regard, we recently reported that rituximab significantly improves the outcome of PMBL, which also displays constitutive NF-κB activity.5

The present study suggests that BCL-6+ DLBCL requires alternative treatment strategies.9,10 We previously reported that the dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH) regimen may be superior to CHOP for DLBCL, suggesting it may overcome additional drug resistance.11,12 To assess its effect in BCL-6− DLBCL, we analyzed etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) in 44 BCL-6+ untreated advanced-stage patients and found an 88% FFS at 43-month median follow-up, suggesting high activity (W.H.W., manuscript in preparation). The Cancer and Leukemia Group B (CALGB) is currently conducting a phase 3 randomized trial of R-CHOP versus DA-EPOCH-R in untreated DLBCLs with microarray to determine if DA-EPOCH-R represents a treatment advance and to investigate tumor biology on outcome.

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Figure 1. BCL-6 mRNA expression among previously defined DLBCL groups.
Response:

Outcomes with R-CHOP in DLBCL leave ample room for improvement

In commenting on our paper,2 Dunleavy and colleagues correctly point out that the outcome for patients with Bcl-6–positive diffuse large B-cell lymphoma (DLBCL) treated with cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab (R-CHOP) still leaves much room for improvement. We agree that the data in Table 5 were misinterpreted, leading Moskowitz to the mistaken conclusion that R-CHOP plus maintenance rituximab (MR) provides a failure-free survival (FFS) of 82%, a result that “will be difficult to improve upon.”2p1198 Rather than a randomized comparison of 4 treatments, this study was a comparison of CHOP and R-CHOP induction, and—for responders only—a comparison of maintenance rituximab and observation (OBS). Table 5 includes only responding patients (ie, a favorable subset) and shows 2-year FFS from the time of second randomization. As reflected in the confidence intervals, there is wide variation, and the numbers are small in the Bcl-6–negative group. While there is no difference in FFS among the 3 rituximab-containing groups, the difference in outcome for the CHOP plus OBS–responding patients according to Bcl-6 expression is nonetheless striking, but will require confirmation in large datasets.

The outcome for patients treated with R-CHOP induction is best seen in Figure 1, based on a weighted analysis removing the effect of MR. As such, these curves should not be labeled with patient numbers and an erratum will be published to remove them. Nonetheless, FFS for the Bcl-6–positive cases leaves ample room for improvement, as suggested by Dunleavy and colleagues. Novel approaches that are based on the biology of the individual disease subsets are required.

Our data underscore the heterogeneity of DLBCL and the need to develop strategies for the different biologic entities that constitute this broad category of non-Hodgkin lymphoma (NHL). We agree that the Bcl-6–positive and Bcl-6–negative groups are molecularly heterogeneous as evidenced by the fact that Bcl-6–positive and –negative cases are represented in both the germinal center B cell–like (GCB) and activated B cell–like (ABC) subsets as shown in Dunleavy et al’s communication. The additional complexity of DLBCL is shown by the results of gene expression studies from the Shipp laboratory demonstrating 3 reproducible subsets of DLBCLs, including a cluster termed B-cell receptor/proliferation that includes both cell-of-origin GCB and ABC subsets.3 We agree that these findings argue strongly for the inclusion of gene expression profiling in the context of DLBCL clinical trials. The current Cancer and Leukemia Group B (CALGB) study includes gene expression profiling on all cases to be performed in Dr Staudt’s laboratory in the National Cancer Institute (NCI) intramural program. This study will establish the feasibility of doing correlative studies on fresh lymphoma specimens within the cooperative groups. Immunohistochemical studies performed on paraffin-embedded tissue, such as those done in our trial, have their own set of issues, including reproducibility of staining and scoring, but may provide valuable information about biology and prognosis without the requirement for fresh tissue.

References


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