Differential Role of BCL2 in Molecular Subtypes of Diffuse Large B-cell Lymphoma

Kieron Dunleavy and Wyndham H. Wilson

Gene expression profiling has been used to divide diffuse large B-cell lymphoma into distinct molecular subtypes with different outcomes following immunochemotherapy. Recently, researchers have shown much interest in investigating the role of biomarkers, such as BCL2, in predicting outcome in diffuse large B-cell lymphoma, particularly in the context of these molecular subtypes. Clin Cancer Res; 17(24); 7505–7. ©2011 AACR.

In this issue of Clinical Cancer Research, Iqbal and colleagues (1) evaluate the prognostic significance of BCL2 in patients with diffuse large B-cell lymphoma (DLBCL) who receive the R-CHOP chemotherapy regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Of interest, they find that BCL2 protein overexpression is a biomarker of poor outcome in the germinal center B-cell (GCB) but not in the activated B-cell (ABC) subtype of DLBCL. Their findings raise interesting questions about the diverse mechanisms of activation of BCL2 in these tumors and about the mode of action and differential activity of rituximab within the GCB and ABC subtypes of DLBCL.

The B-cell leukemia/lymphoma-2 gene (BCL2) was discovered more than 25 years ago through its association with the t(14:18) translocation in follicular lymphoma (2). This cytogenetic abnormality, which leads to deregulated expression of the BCL2 protein, was found in the majority of follicular lymphomas and in a variable number (10%–40%) of de novo DLBCLs (3). Then, with the identification of this gene came the discovery of a family of structurally related proteins that function as important regulators of apoptosis (4). In DLBCL, the inhibitory action of BCL2 on apoptosis was hypothesized to be a cause of chemotherapy resistance, and this notion was supported by several clinical studies in the pre-rituximab era that showed an inverse correlation between BCL2 protein expression and survival (3, 5). Studies done in the post-rituximab era, however, raised the question of whether BCL2 remains a biomarker of treatment failure, and many studies have shown that this is no longer the case (6, 7).

In that regard, looking at the role of BCL2 in molecular subtypes of DLBCL is an interesting undertaking. Iqbal and colleagues (1) investigated the impact of BCL2 protein and mRNA expression on survival within molecular subgroups of DLBCL treated with immunochemotherapy. Their study has 2 notable strengths. First, they used the gold standard method, gene expression profiling, to categorize tumors into GCB or ABC subtype, which eliminates the potential inaccuracies of immunohistochemical algorithms to predict the cell of origin. Second, they focused on a homogeneous population, in that all patients received R-CHOP, and a central expert pathology review was performed. Although studies in the pre-rituximab era by Iqbal and colleagues, as well as other investigators, showed that BCL2 protein overexpression is prognostic only in the ABC subtype, here they find the opposite—that BCL2 protein overexpression is significantly associated with an inferior outcome in the GCB subtype (8). At the mRNA level, although high expression predicted lower event-free survival in DLBCL overall, there was only a trend toward inferior survival in the GCB subtype, which may reflect the fact that mRNA expression may not translate to protein expression.

The results of Iqbal and colleagues raise interesting questions about the mechanisms of BCL2 activation and how these mechanisms may or may not be abrogated by the addition of rituximab to chemotherapy. In the ABC subtype, BCL2 expression is associated with constitutive activation of the NF-κB pathway (9). The mode of action of rituximab in the ABC subtype is poorly understood; however, in vitro studies have shown that it can downregulate NF-κB by induction of the Raf-1 kinase inhibitor protein (a negative regulator of the pathway) and that this mechanism may also occur in vivo and lead to reduced expression of BCL2 (10). It is also possible that rituximab modulates other pathways associated with BCL2 in the ABC subtype.

In the GCB subtype, the presence of a t(14:18) translocation accounts for the overexpression of BCL2 in most (but not all) cases. Of interest, in this study, Iqbal and colleagues find that a t(14:18) translocation is not associated with the adverse outcome seen in the GCB subtype, suggesting that GCB cases with t(14:18) likely have variable levels of BCL2 protein and that some GCB cases without t(14:18) also express BCL2 (Fig. 1). The latter cases are likely to have much higher expression of BCL2 than do translocated cases. The findings of Iqbal and colleagues suggest that rituximab...
does not overcome BCL2-associated resistance in GCB tumors, and thus raise a number of interesting questions with regard to the mechanisms of BCL2 expression and other associated biologic events. For example, the coexistence of BCL2 translocations with other cytogenetic abnormalities, such as those involving MYC and/or BCL6, may be important contributors to treatment resistance (11). Although we have limited clinical experience with these so-called double- and triple-hit tumors, the coexistence of 2 or more mutations is known to be clinically associated with a high rate of treatment failure, even in the immunochemotherapy era. In this regard, it would be interesting to know the frequency of these mutations in this series. The role of BCL6 gene expression, which is generally high but variable in the GCB subtype, could be another covariable in BCL2-positive cases (Fig. 1).

It is possible that BCL2 expression is a surrogate biomarker for several other biologies. As the authors note, the BCL2-negative cases were associated with a favorable microenvironment signature, termed the stromal-1 signature (12). This signature contains genes related to extracellular-matrix deposition and mesenchymal and histiocytic cell infiltration, and it is found in varying proportions with the so-called stromal-2 signature, which contains genes related to endothelial cells and important regulators of angiogenesis and which is associated with an adverse outcome. On the other hand, the BCL2-negative group was associated with higher proliferation, which has been identified as an adverse prognostic signature. In contrast, the BCL2-positive GCB tumors were associated with increased infiltrating follicular helper T cells, which the authors speculate may protect the tumor cells against apoptosis, possibly through downregulation of BIM, as described with follicular-dendritic cells. These varied biologic associations in BCL2-positive and BCL2-negative GCB tumors highlight the inherent drawbacks of such correlative studies and the difficulty of identifying the important mechanisms of drug resistance. These results point to BCL2 as the obvious druggable target in GCB DLBCL and to the high-affinity inhibitor of BH3-only proteins, Navitoclax (ABT-263; Genentech/Abbott), as a prime candidate for testing.

In conclusion, Iqbal and colleagues’ study highlights the importance of evaluating biomarkers in the context of molecular subtypes, and it shows that distinct mechanisms of BCL2 activation (even within a molecular subtype) are associated with different prognoses. The investigators’ findings suggest that some GCB tumors with BCL2 overexpression may benefit from therapies that directly target the BCL2 complex and overcome the inhibitory effects on apoptosis of BCL2. Many of these agents are currently in development (13). Although BCL2 is a useful prognostic marker in subtypes of DLBCL, its expression likely reflects many different mechanisms that drive tumor survival, and it is key to pair clinical investigation and tumor biology for the clinical development of new targeted agents.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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