Improving Our Use and Understanding of Antibodies in B-cell Lymphomas

By

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Atlanta, Georgia | February 11, 2010

Financial Disclosure: Dr. Flowers is a consultant for Genentech, Biogen Idec, Intellikine, Celgene, Millennium, Abbott, and Prescription Solutions.

In this review, Ujjani and Cheson present a useful overview of the array of existing and developing roles for monoclonal antibodies in the management of B-cell non-Hodgkin lymphomas (NHLs). These roles may be characterized as single-agent antibody therapy, use in combination with chemotherapy and/or other antibodies, and use following an initial regimen (consolidation/maintenance). Rituximab (Rituxan), the first monoclonal antibody approved for B-cell NHL, clearly has had greatest application in each of these arenas, but it has now been joined by alemtuzumab (Campath) and ofatumumab (Arzerra) as approved single-agent therapies. Also highlighted are a number of other antibodies aimed at B-cell targets: veltuzumab, GA101, AME-133 (CD20), epratuzumab (CD22), lumiliximab (CD23), galiximab (CD80), dacetuzumab (CD40), mapatumumab, lexatumumab (TRAIL), and approaches to improve antibody therapy such as conjugation with radioisotopes or toxins.

Within this alphabet soup of antibody therapy it remains uncertain what targets, patient populations, and regimens will promote additional approvals for the treatment of NHL. Of note are the limited numbers of clinical studies addressing the pharmacokinetics and
pharmacodynamics of monoclonal antibodies, both when antibodies are used alone and when they are used in combination with chemotherapy or other antibodies. For instance, while rituximab is known to eradicate CD20+ malignancies through a variety of mechanisms—including antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and modifications of the cellular signaling pathways leading to apoptosis—the relative importance of each of these mechanisms in vivo for each lymphoma subtype, each dosing regimen, and each chemotherapy combination is largely unknown. Developing and performing such assays is not trivial, but is critical to improving our understanding and use of antibodies in lymphoma.

**Maintenance Rituximab**

The authors also describe several studies that have evaluated the use of rituximab as maintenance therapy. They detail approaches involving maintenance rituximab following single-agent rituximab, standard chemotherapy (CVP [cyclophosphamide, vincristine, and prednisone]), and rituximab-containing regimens as initial therapy or in the setting of relapse, and note that the type and effect of rituximab maintenance varies substantially across studies. They omit the fact that in the US Intergroup trial, failure-free survival was significantly prolonged ($P = .0004$) for diffuse large B-cell lymphoma (DLBCL) patients who received maintenance rituximab after CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone).[1] However, this finding is only of benefit for patients who could not or did not receive rituximab with their initial therapy and subsequently are able to receive maintenance rituximab, making it of little importance in the current era of rituximab-chemotherapy combinations.

While this trial also demonstrated that maintenance rituximab after rituximab plus CHOP (R-CHOP) was of no benefit for patients with DLBCL, the clinical benefits of maintenance rituximab after initial therapy with rituximab and chemotherapy for follicular lymphoma (FL) and current patterns of maintenance use following rituximab-chemotherapy are yet to be determined. The first of these questions soon will be addressed when early results from the international Primary Rituximab and Maintenance (PRIMA) trial are presented. These findings and other findings described by the authors should help define roles for maintenance therapy with other monoclonal antibodies as well.

Shortly following development of rituximab for FL, it was applied to other B-cell NHLs and in combination with chemotherapy. The authors document the benefits of adding rituximab to chemotherapy regimens for FL, DLBCL, mantle cell lymphoma, and chronic lymphocytic leukemia. Similar benefits have been observed in nearly every other randomized trial involving CD20+ malignancies. Combinations of other antibodies with chemotherapy also are well-described in this review. Among those mentioned, intriguing combinations include antibody doublets with chemotherapy such
as epratuzumab with R-CHOP and FCR (fludarabine, cyclophosphamide, and rituximab) plus lumiliximab.

**Future Trials**

The degree to which the benefits of adding rituximab to chemotherapy is a class effect that would be observed with other anti-CD20 antibodies (or other B-cell–targeted antibodies) is unknown, and will remain so unless randomized trials comparing rituximab plus chemotherapy to another antibody plus chemotherapy are performed. Given the results of the studies described, rituximab-chemotherapy combinations may have set the bar sufficiently high that such studies will not be performed as pathways to drug approval. Notably, the Eastern Cooperative Oncology Group (ECOG) has proposed a comparison of the epratuzumab plus R-CHOP combination to R-CHOP, and FCR plus lumiliximab has been compared with FCR, so studies of adding antibodies may still be feasible. While the benefits of combining rituximab with chemotherapy are significant, additional research is needed to discern the patterns of adoption of combination therapy in the United States across lymphoma subtypes as well as to determine what factors influence who receives rituximab with chemotherapy in practice.

Moreover, the combination of antibodies with chemotherapy regimens has been predominantly empirical, owing to the limited overlapping toxicity profiles. Future rational combinations need to be based on proposed and testable mechanisms of synergy or additive effects. For instance, in vitro studies suggest that modifications of cellular signaling pathways by rituximab are important when this antibody is used in combination with chemotherapy. Dr. Jazirehi and colleagues demonstrated that monomeric rituximab, via negative regulation of the NF-κB and ERK1/2 MAPK pathways reduces the expression level, transcription, and translation of their common downstream antiapoptotic gene product Bcl-X<sub>L</sub>.[2] In Ramos and Daudi cell lines, the ability of rituximab to sensitize cells to paclitaxel, platinum, etoposide, and doxorubicin is abrogated when cells are stably transfected with a Bcl-X<sub>L</sub> overexpressing construct,[2] suggesting the importance of Bcl-X<sub>L</sub> in rituximab-mediated sensitization to chemotherapy. This mechanism of resistance may highlight a role for inhibition of Bcl proteins in overcoming resistance to rituximab and possibly other antibody-based regimens. However, resistance patterns may differ across lymphoma subtypes and when antibodies are used as single agents or with chemotherapy. Therefore, multiple models of antibody resistance are needed.

**Conclusions**

Although rituximab and rituximab-chemotherapy regimens have revolutionized treatment strategies for patients with B-cell lymphomas, relapse remains a consistent
clinical problem. In particular, although DLBCL is commonly cured with R-CHOP, data from the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL study) indicate that early relapses following upfront rituximab-chemotherapy have a poor prognosis and response rate to second-line rituximab-containing regimens.[3] Understanding mechanisms by which malignant B cells become rituximab-resistant and defining means to address these mechanisms may provide pathways for approval of novel antibodies. Moreover, defining the biology of resistance and activity for various antibodies across lymphoma subtypes will become increasingly important as we attempt to select among antibodies and antibody-based regimens in the future.

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References

