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Monoclonal antibodies targeting CD20

Chien-Hsing Chang, Edmund A. Rossi and David M. Goldenberg*

Immunomedics, Inc.; Morris Plains, NJ USA

We are commenting on the article by Klein et al. on the functional properties of several anti-CD20 monoclonal antibodies (mAbs) in the January/February 2013 issue of *mAbs*.[1] Rituximab, the first monoclonal antibody approved for cancer therapy, has truly revolutionized the treatment of a variety of CD20$^+$ hematological malignancies,[2,3] and also has been studied in a large number of autoimmune diseases.[4] It is therefore expected that improved versions of anti-CD20 mAbs are being developed and evaluated clinically as potential next-generation agents. In this regard, the review by these authors is timely, since a number of promising mAbs have been reported and are in various stages of development. How they can be distinguished is important to appreciate and to build on for future innovations. However, in a task of this breadth, it is mandatory that the authors present an accurate and balanced view, especially since they are involved with the development of GA101 (obinutuzumab).

Veltuzumab (hA20, Immunomedics, Inc.) is described in the article as a Type 1 humanized anti-CD20. In contradiction to their statement that it "shows similar specificity, avidity and in vitro activity" to rituximab,[1] we point out that our most recent article elucidating structure-function relationships, cited by these authors, showed that the substitution of asparagine by aspartic acid in the CDR-H3, together with human framework regions from epratuzumab, our anti-CD22 humanized mAb, resulted in significantly slower off-rates compared with rituximab in 3 human lymphoma cell lines.[5] Indeed, back-mutation studies confirmed that the differentiation of the off-rate between veltuzumab and rituximab is related to this single amino acid difference in CDR-H3.[5] In addition, complement-dependent cytotoxicity was more potent in 1 of 2 cell lines, and in vivo, veltuzumab had superior efficacy in 3 human lymphoma xenografts models, compared with rituximab.[5]

The ultimate test of a new agent is its clinical performance, and it is therefore disappointing that Klein et al. did not mention how these different anti-CD20 types and constructs perform in patients, to the extent that data are available. Although some, such as obinutuzumab and ofatumumab, are claimed to have high potency, it is a concern that much higher doses than those used for rituximab were chosen to show superior efficacy.[6-8] At these doses, obinutuzumab may have more toxicity, particularly neutropenia. Indeed, proper comparisons require candidate new mAbs be given in similar or even lower doses and schedules to prove superiority to rituximab. Where direct comparisons to rituximab are being conducted, it would seem reasonable to require that the doses being given by both agents are the same, or at least at a comparable saturation.

Initial clinical studies with veltuzumab have shown that doses as low as 80 mg (for the subcutaneous formulation) or 80 mg/m^2 (for IV infusions) weekly × 4 resulted in comparable rates of objective response (44–47%) to published data for rituximab, but much higher CR/CRu rates (24–27%) mostly in relapsed follicular non-Hodgkin lymphoma patients,[9,10] as predicted from the preclinical studies.

Further, other reengineered forms of anti-CD20 mAbs with improved therapeutic properties have been described, such as multivalent constructs, bispecific mAbs (targeting CD20 and CD22 or CD74), and anti-CD20 immunocytokines, as reviewed recently.[11] Whether these have any advantages over rituximab, however, must await clinical assessment at doses comparable, or lower, to those conventional for rituximab.

Disclosure of Potential Conflicts of Interest

All authors are employees and shareholders of Immunomedics, Inc.

*Correspondence to: David M. Goldenberg; Email: dmg.gscancer@att.net
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