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Rituximab: Therapeutic Benefit! Vitamin R?

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Introduction

On November 26th, 1997, a little-known monoclonal antibody called rituximab was approved by the US Food and Drug Administration for the treatment of relapsed/refractory non-Hodgkin lymphoma (NHL). Over a decade later, rituximab has become one of the biggest therapeutic advancements in the treatment of lymphoid malignancies, redefining the standard of care for a vast majority of B-cell neoplasms. Both as a single agent and in combination with cytotoxic chemotherapy, rituximab has significantly improved response rates and progression-free survival in a variety of lymphoid malignancies, as well as overall survival and cure rates in aggressive NHL. Rituximab has also demonstrated considerable utility in a number of autoimmune hematologic and rheumatologic diseases, and is increasingly being turned to as a well-tolerated, relatively safe, and often less invasive alternative to traditional therapies for these conditions. In fact, rituximab has demonstrated safety and activity in so many diseases that it has been nicknamed “vitamin R”! All joking aside, as much as the use of rituximab has enhanced treatment options, there are still many unanswered questions and opportunities for further improvement remain aplenty.

Despite a decade of experience, rituximab has preserved a certain “magical” quality. First of all, there is the experience that it can be safely added to virtually any treatment. Who would have ever thought that a drug which essentially obliterates an entire arm of the immune system for extended periods of time, could be as safe as rituximab has proven to be? Furthermore, rituximab can be combined with virtually any existing treatment strategy without significantly increased toxicity. –In this regard we may in fact have been spoiled and other monoclonal antibodies or targeted agents may not necessarily be so safe and unproblematic to integrate into existing treatment regimens.

In addition to rituximab’s safety profile, uncertainties about its mechanism of action, controversies about optimal dosing**,** and unique and still only partially appreciated aspects of its pharmacokinetics add to the “magic”. With regard to mechanism, we know that rituximab binds to the large extracellular loop of CD20 on the surface of B-cells and depletes them. We know that cell death can occur through complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and (in some experimental systems) direct signaling. We still do *not* know, however, exactly how these mechanisms interface and affect each other within different tissue compartments, or how important each mechanism is individually within the context of a given disease. We also do not know whether we are maximizing efficacy and minimizing drug resistance with the current standard dose of 375mg/m2. With regard to

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efficacy, a recent study using a murine lymphoma model demonstrated a clear association between high tumor burden and both low post-infusion rituximab serum levels and inferior response,[1] a finding that raises the possibility that we may in fact be underdosing some patients with high burdens of disease by using a dose that is adjusted only for body surface area. With regard to drug resistance, recent attention has been paid to "CD20 shaving", a process whereby rituximab/CD20 immune complexes on malignant B cells are removed by FcγR-expressing effector cells, essentially rendering a significant portion of residual disease CD20-negative and thus refractory to subsequent rituximab treatment.[2] It is thought that saturation/exhaustion of B-cell clearance mechanisms may lead to CD20 shaving. Given concerns over both insufficient dosing in the presence of high tumor burden and mechanisms of drug resistance related to bolus dosing, it may come as no surprise that some investigators have explored massively increased doses of rituximab to increase efficacy,[3,4] while others have studied a metronomic approach of frequent low doses of rituximab to avoid CD20 loss.[5,6] A more complete understanding of the *in vivo* pharmacokinetics and pharmacodynamics of rituximab may pave the way to even greater efficacy than currently possible. Time and well designed studies will tell.

This edition of *Seminars* begins with detailed discussions of the CD20 molecule and the mechanisms of action of and resistance to rituximab, followed by reviews of its use in low-grade lymphomas, high-grade lymphomas, CLL, and autoimmune hematologic disease. These reviews provide a comprehensive overview of the clinical use of rituximab to date, as well as food for thought regarding some of the most pertinent unanswered questions regarding its use. Attention is then devoted to the phenomenon of "late-onset" rituximab-associated neutropenia, followed by a review of rituximab-associated infections. Lastly, we are given an exciting glimpse into the future with a discussion of novel anti-CD20 antibodies that hold the potential for even greater efficacy.

As John F. Kennedy once said in regards to scientific progress, "The greater our knowledge increases, the greater our ignorance unfolds." Rituximab, a product of remarkable advances in biomedicine, has become a highly effective instrument in the treatment of hematologic diseases. At the same time it has exposed areas of ignorance, which have stimulated new discoveries that will further improve treatment options for our patients.

References

1. Dayde D, Ternant D, Ohresser M, et al. Tumor burden influences exposure and response to rituximab: pharmacokinetic-pharmacodynamic modeling using a syngeneic bioluminescent murine model expressing human CD20. Blood 2009;113:3765–3772. [PubMed: 19029438]
2. Beum PV, Kennedy AD, Williams ME, Lindorfer MA, Taylor RP. The shaving reaction: rituximab/CD20 complexes are removed from mantle cell lymphoma and chronic lymphocytic leukemia cells by THP-1 monocytes. J Immunol 2006;176:2600–2609. [PubMed: 16456022]
3. Byrd JC, Murphy T, Howard RS, et al. Rituximab using a thrice weekly dosing schedule in B-cell chronic lymphocytic leukemia and small lymphocytic lymphoma demonstrates clinical activity and acceptable toxicity. J Clin Oncol 2001;19:2153–2164. [PubMed: 11304767]
4. O'Brien SM, Kantarjian H, Thomas DA, et al. Rituximab dose-escalation trial in chronic lymphocytic leukemia. J Clin Oncol 2001;19:2165–2170. [PubMed: 11304768]
5. Aue G, Lindorfer MA, Beum PV, et al. Fractionated subcutaneous Rituximab is well tolerated and preserves CD20 expression on tumor cells in patients with chronic lymphocytic leukemia. Haematologica. 2009
6. Williams ME, Densmore JJ, Pawluczkowycz AW, et al. Thrice-weekly low-dose rituximab decreases CD20 loss via shaving and promotes enhanced targeting in chronic lymphocytic leukemia. J Immunol 2006;177:7435–7443. [PubMed: 17082663]