Review of Antibody-Based Immunotherapy in the Treatment of Non-Hodgkin Lymphoma and Patterns of Use

Andrew C. Cannon, Fausto R. Loberiza, Jr

Abstract

The creation of new cancer immunotherapies represents 1 of the most exciting advances taking place this decade. Although clinical studies continue to indicate improvement in clinical outcomes, the speed of its diffusion into actual practice is not known. It is important to understand practice variation in the use of recommended immunotherapies as new and more effective immunotherapies are developed. Additionally, as the field continues to grow, immunotherapy will encounter new barriers that will hinder its rapid adoption into clinical practice. This review aims to present a brief summary of the mechanisms and uses of antibody-based immunotherapies used to treat lymphoma and to present available practice variation data, including factors associated with variation. Review of the available data implicated patient characteristics and health care systems as being associated with practice variation; however, in several instances, ease of use, cost, toxicity, and physician knowledge contributed to variation, regardless of efficacy. As new immunotherapies are developed, these factors must be considered to increase the rapid diffusion of effective immunotherapies into wide clinical use.

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Introduction

The meteoric success of rituximab inspired an upsurge in both the development of new immunotherapies and the methods used to test them. The newer approved immunotherapies exhibit a level of mechanistic complexity previously unseen in successful immunotherapies: rather than targeting antigens presented on the surface of malignant cells, these drugs serve to bolster the host's antitumor immune response.[1,2] However, as new and more effective immunotherapies are developed, the field will encounter new barriers that can hinder the rapid adoption of these treatment modalities. Thus, data concerning the practice variation in the use of existing antibody-based immunotherapies are valuable for understanding the challenges that newly developed immunotherapies may face. The use of immunotherapy to treat non-Hodgkin lymphoma (NHL) offers a particularly important tool in that immunotherapy—in the form of rituximab—has been a core component of the standard of care for a large proportion of NHL cases for more than a decade. However, at the same time, many antibody-based immunotherapies designed to treat various forms of NHL continue to be underused despite, in some cases, very promising clinical trials. This review aims to present a brief summary of the mechanisms and specific uses of antibody-based immunotherapies (Table 1) to treat NHL as well as available practice variation data, including the complex factors associated with variations.

Section of Oncology/Hematology, Internal Medicine, University of Nebraska Medical Center, Omaha, NE

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Address for correspondence: Fausto Loberiza, Jr, MD, MS, Section of Oncology/Hematology, Department of Internal Medicine, University of Nebraska Medical Center, 987680 Nebraska Medical Center, Omaha, NE 68198-6520, Fax: 402-559-6520; e-mail contact: floberiza@unmc.edu

Rituximab

The US Food and Drug Administration (FDA) approval of rituximab in 1997 made it the first monoclonal antibody (mAb) approved for the treatment of human malignancy. Rituximab is a chimeric antibody with a mouse variable region from the α-CD20 antibody ibritumomab and the human IgG1 κ constant regions.[3] CD20 is not internalized or shed by the cell, and it is expressed by all B-cell malignancies except acute lymphoblastic leukemia and multiple myeloma.[3,4] Finally, CD20 overexpression is associated with resistance to apoptosis.[3] This combination of characteristics makes CD20 an effective target for mAb-based immunotherapy.

Several different mechanisms have been attributed to the anticancer effects of rituximab. The chimeric antibody was chosen specifically for the purpose of increasing complement-mediated cytotoxicity (CMC) and antibody-dependent cell-mediated

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cytotoxicity (ADCC), which are the main mechanisms through which rituximab produces its antitumor effect.[5] Additionally, reports of increased cytotoxic T-cell response against the malignant clone in patients treated with rituximab suggest that rituximab may induce vaccine-like effects.[6] Finally, there is considerable evidence that the binding of rituximab to CD20 has the capability of interfering with a variety of intracellular processes, including Bcl-2 signaling, BCR signaling, and caspase signal cascades.[5]

As a single agent, rituximab treatment produced durable response rates (RRs) in a large variety of cancers, including treated and untreated follicular lymphoma (FL), relapsed indolent lymphoma, relapsed diffuse large B-cell lymphoma (DLBCL), relapsed and untreated mantle cell lymphoma (MCL), and relapsed and untreated chronic lymphocytic lymphoma/small lymphocytic lymphoma (CLL/SLL), among others. Dillman presented summaries of all single-agent rituximab trials.[7] Rituximab has also been used with some success in the maintenance, consolidation, or salvage therapy (or a combination) of FL and CLL/SLL after high-dose chemotherapy,[8] as well as DLBCL and MCL after autologous hematopoietic stem cell transplantation.[9,10]

The most important use of rituximab is in combination with chemotherapy. In patients with untreated CLL, RRs near 95% were observed in key trials of rituximab plus cyclophosphamide and fludarabine.[11-13] Additionally, rituximab was shown to improve outcomes of patients: 65% and 87% of the rituximab arm experienced 3-year progression-free survival (PFS) and overall survival (OS), respectively, compared with the control arm, which had 45% and 83% PFS and OS, respectively. For treatment of patients with relapsed or refractory CLL, RRs of 53% to 93% were observed for rituximab plus chemotherapy.[12,13] This study also observed an increase in the median PFS of patients in the rituximab arm to 30.6 months compared with 20.6 months in the control arm.

When rituximab was used in combination with chemotherapy to treat previously untreated FL, RRs between 81% and 96% were observed depending on the chemotherapy regimen used.[8,13-17] Furthermore, in each case, the overall RR was greater for rituximab plus chemotherapy than for chemotherapy alone.[14-17] In phase III trials, the addition of rituximab to chemotherapy was shown to have a significant impact on overall survival; 3 phase III trials showed increases in OS ranging between 5% and 13% for the groups that received rituximab plus chemotherapy over the chemotherapy-alone groups.[15-17] Finally, another phase III trial of rituximab in relapsed or refractory FL showed an increase in PFS when rituximab was added to chemotherapy (median PFS not reached at 3 years vs. 21 months for chemotherapy alone).[18]

In the first-line treatment of MCL, rituximab in combination with chemotherapy was capable of producing high RRs (ranging from 94%-97%), increasing the proportion of patients experiencing 3-year failure-free survival (64% chemotherapy plus rituximab vs. 10%-24% historical control)[19] and extending the time to treatment failure by approximately 7 months.[20] Trials focusing on relapsed MCL after CHOP (cyclophosphamide, doxorubicin [hydroxydaunorubicin], vincristine [Oncovin], and prednisone) showed RRs of 60% to 70% and PFS ranging from 23 to 25.6 months.[21-23] One phase III trial showed that the addition of rituximab to chemotherapy compared with chemotherapy alone increased OS; the median OS of the chemotherapy plus rituximab cohort had not been reached at 3 years compared with 11 months for chemotherapy alone.[18]

Initial treatment of DLCBL with rituximab plus chemotherapy was shown to have RRs ranging from 76% to 94%.[24-27] Furthermore, the addition of rituximab to chemotherapy, compared with chemotherapy alone, for the treatment of DLBCL in young relatively healthy patients was shown to increase 3-year event-free survival (79% vs. 59%) and 3-year OS (93 vs. 84%).[26] Finally, addition of rituximab to chemotherapy for treatment of DLBCL in the elderly was shown to decrease the risk of death by 47% compared with chemotherapy alone.[25]

Rituximab is now the standard first-line treatment for patients with CD20-positive ($CD20^+$) B-cell malignancies and is frequently administered in maintenance, consolidation, and salvage settings for patients with FL and CLL (for information on common and serious adverse reactions to rituximab and other immunotherapies discussed here see Table 2).

Ofatumumab

Ofatumumab is a human IgG1 κ α-CD20 antibody. The sole difference regarding mechanism between rituximab and ofatumumab is the binding site. Of the 2 extracellular loops on CD20, rituximab binds 1, whereas ofatumumab binds the other in addition to an intracellular loop that transiently approaches the outer membrane.[28,29] It is believed that these differences are in part responsible for tighter binding of ofatumumab compared with rituximab, resulting in increased exposure of the antibody Fc domain and thereby enhancing CMC and ADCC[30-32]; in fact, in vitro studies show increased CMC induced by ofatumumab compared with rituximab.[28,29,31,33]

In 2009, ofatumumab was granted FDA approval for the treatment of CLL that is considered refractory to fludarabine and alemtuzumab. Early studies of ofatumumab in combination with chemotherapy for the treatment of relapsed or refractory CLL found RRs ranging from 40% to 77% depending on exposure to rituximab and chemotherapy regimen.[34-37] Furthermore, these studies reported widely variable median PFS, ranging from 5.3 months to 23.6 months. However, these values appear to be similar if not better than those produced by rituximab under similar conditions. A head-to-head comparison of the 2 antibodies in CLL and other diseases would be interesting, but the already high RRs and PFS produced by rituximab would make it difficult to achieve statistical significance.

Ofatumumab has also been tried in the first-line treatment of CLL with some success. Two studies reported overall RRs of 77% and 96% when used in combination with fludarabine and cyclophosphamide or fludarabine and pentostatin and cyclophosphamide, respectively.[38,39] In these trials, the complete remission (CR) rate was near 50%. Furthermore, comparison between chemoimmunotherapy with ofatumumab versus chemoimmunotherapy with rituximab in this study revealed that the ofatumumab group had greater 2-year treatment-free survival (86% vs. 68%).[39]

Finally, ofatumumab has been tried in a variety of other settings with some success. One study evaluated ofatumumab in combination with CHOP as first-line treatment of FL. Here the authors reported an overall response between 90% and 100%, depending on dose, and a CR rate of 62%.[40] In relapsed FL in patients who