Radioimmunotherapy: A New Treatment Modality for B-Cell Non-Hodgkin's Lymphoma

Review Article [1] | May 01, 2004
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We applaud Ghobrial and Witzig for their comprehensive and balanced article on "Radioimmunotherapy: A New Treatment Modality for B-cell Non-Hodgkin's Lymphoma." These authors have provided a review that will serve the oncologist and oncology patient well. They have not engaged in arcane and tedious discussion of which anti-CD20 monoclonal antibody (ibritumomab tiuxetan [Zevalin] or tositumomab/iodine-131 [I-131] tositumomab [Bexxar]), or radionuclide (yttrium-90 [Y-90] or I-131), or dosing method is better. Wisely, Ghobrial and Witzig have provided accurate distillates of the many publications on these exciting drugs. Because no rigorous body of data clearly indicates that one drug is better than the other, these debates only confuse the oncologist and are better left to the "technocrat."

New Treatment Paradigm

What is important to the oncologist and patient with non-Hodgkin's lymphoma (NHL) is that a paradigm change has occurred. After decades of adding chemotherapy drugs and regimens without altering therapeutic outcomes,[1] the management of NHL has been dramatically influenced by monoclonal antibodies. Whether used for immunotherapy or radioimmunotherapy, three anti-CD20 monoclonal antibodies have recently been approved because of their remarkable therapeutic effects in patients with chemotherapy-resistant, low-grade NHL.[2-4] Radioimmunotherapy is a method by which systemic radiotherapy is delivered to malignant cells using monoclonal antibodies, which target NHL antigens, as carriers of therapeutic radionuclides like Y-90 or I-131. Reflecting the impact of the radiation from the radionuclide, overall response rates and complete remission rates were two to four times greater for Y-90-labeled ibritumomab tiuxetan, compared to rituximab (Rituxan), the anti-CD20 monoclonal antibody alone, in the randomized, pivotal trial.[3] Similar therapeutic outcome enhancements were reported for tositumomab/I-131-labeled tositumomab, as compared to the most recent chemotherapy regimen that the patient had received.[4] Whereas rituximab immunotherapy for NHL quickly came into widespread use after its approval, it should be noted that radioimmunotherapy using tositumomab/I-131 tositumomab or ibritumomab tiuxetan has thus far been slow to be incorporated into the management of NHL.

Toxicity and Logistics

It is appropriate to ask the question, "Why the difference?" Clearly the efficacy profile of ibritumomab tiuxetan has been shown to be superior to that of rituximab,[3] and that of tositumomab/I-131 tositumomab to the most recent chemotherapy regimen.[4] While much is made of the toxicity associated with radioimmunotherapy, it has proven highly attractive to patients in contrast to chemotherapy. Furthermore, there is no substantive toxicity argument.[5,6] It is an advantage that the hematologic toxicity develops slowly and predictably after radioimmunotherapy. Neutropenic sepsis and bleeding are rare, in contrast to the frequency of such events seen with chemotherapy.[3,4] Subsequent treatment has been shown to be practicable and uncomplicated despite somewhat protracted duration of the hematologic toxicity after radioimmunotherapy.[7,8] Logistic considerations are sometimes offered as an impediment to radioimmunotherapy. Although the drugs must be specially ordered, they are readily available. It is true that a second specialist, the nuclear medicine physician, must be involved in the same way that the radiation oncologist must be involved when the NHL patient requires local radiotherapy. Nevertheless, ibritumomab tiuxetan and tositumomab/I-131 tositumomab have been shown to present minimal radiation safety issues for
health-care personnel and society, and these considerations are readily managed.[9] Superior Results to Standard Therapy

All things considered, we must acknowledge that the management of low-grade NHL has been remarkably improved in recent years because of the availability of new drugs, including monoclonal antibody-based drugs.[10-14] As a single agent, rituximab is less effective in aggressive NHL. Ibritumomab tiuxetan and tositumomab/I-131 tositumomab are effective in transformed and aggressive NHL[4,5,15]; another I-131-labeled antilymphoma monoclonal antibody (Lym-1) was particularly effective in treating diffuse large-cell NHL.[16] The therapeutic efficacy/safety profiles of radioimmunotherapy are highly attractive to the informed patient and physician, so there is no basis for deferring the use of ibritumomab tiuxetan and tositumomab/I-131 tositumomab. To the contrary, evidence of high response rates associated with durable remissions and excellent quality of life suggest that the treatment algorithm for the management of patients with NHL should include these drugs at an early stage. As a single agent given in a single dose to previously untreated patients with advanced follicular lymphoma, tositumomab/I-131 tositumomab provided an overall response rate of 95% and a complete remission rate of 74%, despite the fact that 63% of the patients had bone marrow involvement.[17] The 5-year progression-free survival for these patients was 62%. Toxicity was minimal, and none of the patients have developed myelodysplastic syndrome to date. And the best is yet to come. The cure of "incurable" NHL is a reasonable expectation with better versions of radioimmunotherapeutic drugs and strategies. Administration of a second dose of radioabeled monoclonal antibody has been shown to convert partial remissions to complete remissions.[16] As might be expected from the experience with chemotherapy and radiotherapy, administration of multiple doses of radiolabeled monoclonal antibodies-referred to as a fractionation strategy-has been shown to be advantageous in preclinical models and in clinical trials.[18] Radiometal chelators, shown to be superior to those currently used, are available to improve conventional radioimmunotherapy.[19,20] Importantly, pretargeting radioimmunotherapy strategies have been shown to provide better therapeutic indices than standard one-step radioimmunotherapy.[21,22] These strategies pretarget a bifunctional monoclonal antibody to the malignant NHL cells followed by the administration of a small radionuclide carrier that quickly penetrates and is concentrated in the malignant cells, or excreted in the urine. Conclusions

In summary, radioimmunotherapy should be incorporated into the fundamental management of patients with B-cell NHL soon after these patients have proven to be incurable. Although remarkable progress has been made since the use of radioimmunotherapy for B-cell malignancies was first reported,[23] readily predictable improvements using better drugs, strategies, and combinations with other drugs are certain to make these approaches integral to the management of patients with NHL.

Disclosures: The authors have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

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Published on Physicians Practice (http://www.physicianspractice.com)


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