

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Will Radioimmunotherapy Survive?

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H&O What are the positive aspects of radioimmunotherapy?

AZ There are two radioimmunotherapeutic agents approved by the US Food and Drug Administration for use in patients with non-Hodgkin lymphoma, both of which target the B-cell antigen CD20: yttrium-90 (Y-90) ibritumomab tiuxetan (Zevalin, Biogen Idec) and iodine 131 (I-131) tositumomab (Bexxar, GlaxoSmithKline). These agents differ in their radioactive moiety but share similar properties insofar as they are highly effective monotherapies, with response rates in the range of 70–80% in relapsed/refractory follicular lymphoma. Both have been shown to be effective in patients who have not responded to or progressed after therapy with rituximab (Rituxan, Genentech/Biogen Idec). In the present era, availability of agents that are effective in the rituximab-refractory population is critically important. Another advantage of the radioimmunotherapies is that treatment is completed within a week.

H&O What are the negative aspects of radioimmunotherapy?

AZ There are practical obstacles to the use of these agents. First, there is significantly more coordination of care needed when these drugs are administered compared to that needed for typical chemoimmunotherapy. The medical oncologist must identify the appropriate patients for these therapies and then refer the patients to a radiation oncologist or nuclear medicine physician, depending on local circumstances. It is thus important that a medical

oncologist be aware of who can administer this therapy in his or her area. Furthermore, after the therapy is completed, side effects can persist. The patient's blood counts need to be monitored for up to 12 weeks because the counts tend to decrease 6–7 weeks after radioimmunotherapy and require 3–5 weeks to recover. Another potential drawback to radioimmunotherapy is its unknown exact contribution to the risk of developing myelodysplasia (MDS) or acute myeloid leukemia (AML). Patients who have received these radioimmunotherapeutic agents have developed myelodysplasia and AML. Evidence suggests that these drugs are not the sole cause of MDS/AML but potentially contribute to the risk in patients with prior extensive chemotherapeutic treatment. In a study of 76 patients treated at the University of Michigan with single-agent radioimmunotherapy as upfront treatment, none has developed MDS/AML. One patient who recurred and then received subsequent treatment did develop MDS later. Radioimmunotherapy can be considered a contributing factor to this risk, but to what degree and in which patients are unknown at present. Nevertheless, oncologists may be reluctant to use these agents due to this risk.

H&O If a patient does develop MDS or AML after receiving radioimmunotherapy, are the treatment options different than if the patient had not received radioimmunotherapy?

AZ No. The nature of the MDS/AML that is observed dictates the therapeutic approach. Patients with the 5q-syndrome are candidates for therapy with lenalidomide

(Revlimid, Celgene), for example. Other treatment options exist for the treatment of MDS, but any patient who develops AML after indolent lymphoma, regardless of having received radioimmunotherapy or only chemotherapy, typically has a poor prognosis. With MDS, patients sometimes have effective palliative options that can reduce transfusion requirements and improve quality of life. Overall, the treatment options for these complications are not affected by prior radioimmunotherapy.

H&O What are the financial obstacles to wider use of radioimmunotherapy?

AZ The obstacles to wider administration of radioimmunotherapy are often thought to include financial considerations. The medical oncologist who can administer rituximab or chemotherapy and receive remuneration for this practice does not have a financial incentive to administer radioimmunotherapy. There is no financial benefit for giving I-131 tositumomab and the benefit is quite limited for giving Y-90 ibritumomab tiuxetan. In my view, however, financial benefit (or lack thereof) is not the greatest barrier to the more widespread use of radioimmunotherapy. Rather, I believe that the wide variety of alternative treatments available means that what is perceived as the most complicated option—radioimmunotherapy—becomes the option of last resort. Clinicians tend to wait to give radioimmunotherapy, and by the time they decide to administer it, the patient has become ineligible for the therapy. The appropriateness of radioimmunotherapy, like that of other second- and third-line treatments, is hampered by low blood counts and packed bone marrow. Clinical situations in which strong therapies are not safe are common as patients relapse, and radioimmunotherapy is similar in this regard to other therapies, but more commonly, clinicians wait to administer it until later in the disease course due to the complexity of its administration.

H&O How might some of these obstacles be overcome?

AZ What is needed to change the way the community thinks about radioimmunotherapy is evidence that this mode of treatment is a fundamentally effective option that changes patients' outcomes. Some hints that radioimmunotherapeutic agents are highly effective come from the trial at the University of Michigan I mentioned by Dr. Mark S. Kaminski and colleagues, which was a small phase II trial with 76 patients. The disease-free and overall survival rates have been excellent. This trial's patient population is fairly typical, based on the patients' prognostic factors. Another promising phase II trial, conducted

by the Southwest Oncology Group (SWOG), administered cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) followed by radioimmunotherapy. Approximately 100 patients were treated in this trial and the results seen are the best CHOP-based results ever reported by SWOG. But the only way to conclusively demonstrate superiority of radioimmunotherapy would be with a randomized trial comparing it to standard of care. The ongoing SWOG 0016 trial, conducted by SWOG and the Cancer and Leukemia Group B, is randomizing patients to be treated with rituximab plus CHOP (R-CHOP) to CHOP followed by radioimmunotherapy with I-131 tositumomab. This trial is expected to be completed in late 2007 or early 2008. A similar randomized trial using Y-90 ibritumomab tiuxetan is ongoing in Europe. If in randomized trials a clear survival advantage, an advantage in remission duration, or an increased time to retreatment is found, I believe there will be a compelling reason for the increased use of these agents. However, I do think the logistical issues will remain an obstacle to the widespread use of these agents even with incontrovertible evidence of their effectiveness.

Additionally, more widespread use of these agents could be enabled by some reforms. For example, endocrinologists can become licensed to administer radio-iodine to patients with thyroid cancer after only 80 hours of training. If medical oncologists could also be licensed to give an arguably safer radio-iodine in the form of I-131 tositumomab, the role of medical oncologists would change and the need for referrals would decrease. Furthermore, once a medical oncologist refers a patient to a radiation oncologist or nuclear medicine physician for radioimmunotherapy and has had the experience of working and communicating with the treatment team, I believe these oncologists tend to use the agents repeatedly. More and better training may lead to more widespread use. The support for reimbursement and preapproval for both products is satisfactory, and there are systems in place to aid practitioners.

H&O What is your outlook for the future of radioimmunotherapy?

AZ Medical oncologists have overlooked radioimmunotherapy thus far. The reasons I mentioned may not explain this situation fully because patients will be referred for allogeneic or autologous stem-cell transplantation or external-beam radiation therapy, other complex and difficult methods of treatment. For some reason, hesitation exists for radioimmunotherapy in particular. Despite my own belief that medical oncologists are relatively well informed about this treatment option due to the availability of data, what seems to be missing is the compelling data from a

randomized phase III trial of radioimmunotherapy after CHOP in comparison to R-CHOP. I am fairly optimistic that if one of the ongoing trials is robustly positive, there will be an impetus for the more widespread application of these drugs. If these trials are only marginally positive, then I would be pessimistic about the survival of these agents in the marketplace, simply because the numbers of patients being treated are not sufficient for the manufacturers' required revenue streams.

Suggested Readings

Bennett JM, Kaminski MS, Leonard JP, et al. Assessment of treatment-related myelodysplastic syndromes and acute myeloid leukemia in patients with non-Hodgkin lymphoma treated with tositumomab and iodine I131 tositumomab. *Blood*. 2005;105:4576-4582.

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Vose JM, Wahl RL, Saleh M, et al. Multicenter phase II study of iodine-131 tositumomab for chemotherapy-relapsed/refractory low-grade and transformed low-grade B-cell non-Hodgkin's lymphomas. *J Clin Oncol*. 2000;18:1316-1323.



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