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ZEVALIN® RADIOIMMUNOTHERAPY FOR EARLY TREATMENT OF CERTAIN TYPES OF NON-HODGKIN'S LYMPHOMA

On February 19, 2002, the FDA approved **Zevalin**® (ibritumomab tiuxetan), a radiolabeled monoclonal antibody, making it the first commercially available radioimmunotherapy for the treatment of patients with certain types of B-cell non-Hodgkin's lymphoma. Radioimmunotherapy (RIT) combines the targeting power of monoclonal antibodies with the cell-damaging ability of localized radiation, creating an excellent modality in the treatment of non-Hodgkin's lymphoma (NHL), which is intrinsically a radiation-sensitive malignancy. The Zevalin therapeutic regimen is indicated in the United States for the treatment of patients with relapsed, or refractory low-grade, follicular, or transformed B-cell NHL, including patients with Rituxan refractory follicular NHL. Extensive clinical studies have confirmed high response rates and durable responses in such patients. When given at 0.4 mCi/kg (maximum dose 32 mCi), Zevalin is safe and effective. Zevalin, developed and marketed in the United States by **Biogen Idec** (Cambridge, MA), is given as a part of a regimen that takes 7 to 9 days to complete, with no requirement for patient hospitalization, isolation, or shielding.

Radioimmunotherapies are manufactured by linking monoclonal antibodies, which are engineered in a laboratory to recognize and attach to substances on the surface of certain cells, to radioactive isotopes. Zevalin is linked with the radioactive isotope yttrium-90 (Y-90). The Zevalin therapeutic regimen consists of a low-dose infusion of Rituxan preceding indium-111 Zevalin, followed 7 to 9 days later by a second low-dose infusion of Rituxan prior to Y-90 Zevalin. Zevalin binds to malignant and normal B-cells, and the energy released from the Y-90 kills target cells and spreads to other nearby cancer cells, as well as some normal cells. Unlabeled pretreatment with Rituxan improves biodistribution, clears the majority of normal B-cells, and increases the specificity by which the Zevalin antibody binds to target cells, thus reducing the toxicity of Zevalin. This form of pretargeted radioimmunotherapy could produce higher response rates than with Zevalin alone, and prove efficacious in more resistant forms of lymphoma.

There have been data suggesting that Zevalin would be more effective if used earlier in treatment, prior to multiple courses of chemotherapy. Data from an integrated analysis presented at the 2003 American Society of Hematology 45th Annual Meeting and Exposition demonstrated that NHL patients receiving second-line treatment with Zevalin experienced higher response rates and longer duration of responses, compared with third-line and later in the treatment paradigm (*1*). Results of the study showed that second-line patients had a higher response rate (86%) than those receiving it as a third-line therapy or beyond (72%) (*2*). The benefits of earlier therapy were particularly remarkable among patients with follicular NHL (*3*). The difference in the complete response rate between the two groups (49% vs. 28%) was even greater (*4*). Second-line patients also had a longer median time to progression (12.6 vs. 7.9 months) and median duration of response (13.7 vs. 8.2 months) (*5*). Times to progression and duration of response in second-line patients reaching a complete response rate were 23.9 and 22.8 months, compared with 15.6 and 14.6 in third-line+ patients, respectively (*6*).

Michael J. Katin, MD, of 21st Century Oncology (Fort Myers, FL), a radiation oncologist with practices throughout the United States, states that it is unfortunate if patients are not offered Zevalin early on in treatment. "It is easy to have continued cycles of systemic chemotherapy or localized areas of radiation therapy without someone realizing that radioimmunotherapy is a treatment option. As a result, some patients' marrow reserves are limited by the time it is suggested. By then, it is not possible to administer the modality, so patients do not get the advantage of it." As further suggested by Dr. Katin, as with almost every treatment,

whether chemotherapy or radiation therapy, the earlier in the course of the illness it is given, the better the response usually is. "If RIT is used earlier in treatment, I think there will be a chance of sorting out those patients who may have an outstanding response [to RIT] and actually get some long-term responders, rather than waiting until it's used as a fifth- or sixth-line treatment." Dr. Katin has treated more than 30 cases with this therapy and it has been shown to be safe in the short term. He noted that the biggest problem encountered is the lack of tolerance in patients who have had extensive prior treatments. "Again, the idea is to bring it into the treatment selection earlier in the course of the disease. We have been impressed that the vast majority of patients have responded to the treatment, and there is a smaller percentage that has an extended long-term response. These are the people we would like to identify better, so we can try to see what characteristics would predispose someone to have an excellent response rather than just a good response."

Brad Pohlman, MD, Director, Lymphoma Program, Cleveland Clinic Foundation (Cleveland, OH), explains, "There is fair amount of data indicating patients are most likely to respond, are most likely to have a complete response, and are most likely to have a durable response if they receive this treatment early in the course of their disease. This is particularly significant with patients who have received only one prior therapy, when compared to patients who have received two or more prior therapies. Further, we know that the myelosuppression, which is the major toxicity from radioimmunotherapy, is more severe and most prolonged in patients who have received more prior therapy. So both from an efficacy standpoint and from a safety standpoint, it makes more sense to administer radioimmunotherapy earlier as opposed to later in the course of the disease."

Because of the many specialties involved when utilizing Zevalin, the relationships established among the medical oncologist, radiation oncologist, and nuclear medicine physician is of the utmost importance. Roger Macklis, MD, Professor and Chair, Department of Radiation Oncology, Cleveland Clinic Foundation, believes that "it is really a three-way alliance when evaluating and making decisions about patients. We have a terrific relationship among our three departments and we work very closely together. The advantage is that each of us is doing that thing for which we are best trained and best experienced. The medical oncologist has the most training in terms of giving systemic therapy. The nuclear medicine physician has experience with the low-level radioisotope infusion and the gamma camera scans. My department is experienced in all kinds of therapy, including radiopharmaceutical therapy. I believe the way we work together is actually the safest for the patient and is the most likely to achieve a good result. We have been doing it this way for a few years and we are going strong. It can be problematic when physicians start doing things that, although in theory they can do, they may not really be fully trained for, and their infrastructure may not be fully equipped for."

Dr. Katin agrees that RIT is perhaps the only type of treatment for which three separate specialties have such important roles other than at the very beginning of the disease. "In this particular disease, patients are going to be followed closely by a hematology oncologist—it's not a disease that the radiation oncologist is going to manage primarily—so they need to be aware of the advantages and the restrictions of the use of radioimmunotherapy. The nuclear medicine physician is involved in the diagnostic phase in terms of seeing the uptake of the antibody to make sure that there is not altered biodistribution which would make it hazardous to use."

Today, Zevalin is being investigated in multiple clinical trials at major medical centers in the United States and in a variety of treatment strategies, including combinations with front-line and second-line chemotherapy regimens and as part of autologous and allogeneic stem cell transplantation. Zevalin also is being investigated as front-line and second-line therapy, with or without combination chemotherapy, in aggressive lymphomas. With Zevalin, new hope for an improved quality of life can be offered to NHL patients.

For more information concerning Zevalin or other Biogen Idec products, call the company at 1-617-679-2000, or visit the company's Web site at www.biogen.com.

References:

1. Emmanouilides, C. *et al*. Abstract #4949, *Blood* 2003;102(11).
2. *Ibid*.
3. *Ibid.*
4. *Ibid*.
5. *Ibid.*
6. *Ibid*.