

ADVANCES IN LLM

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Section Editor: Susan O'Brien, MD

Radioimmunotherapy in Follicular Lymphoma: An Update



Joseph R. Mace, MD
Florida Cancer Specialists
Saint Petersburg, Florida

H&O What are the traditional treatment options for follicular lymphoma (FL) patients?

JM Treatment planning and recommendations for newly diagnosed FL must take into account the patient's presenting stage, histologic grade, Follicular Lymphoma International Prognostic Index (FLIPI) score, as well as the presence of referable symptoms. The newly diagnosed patient who presents with no significant symptoms and favorable prognostic features can be monitored without immediate treatment. This "expectant observation" approach is predicated upon the incurability of disease for the vast majority of patients, coupled with the potential toxicities associated with treatment in a patient who is otherwise feeling well. However, well-tolerated targeted therapies, including monoclonal antibody therapy, immunotherapy, and radioimmunotherapy (RIT), are challenging this traditional paradigm. It is also important to note that although a significant percentage of patients will not require immediate therapy, individual patient characteristics impact the degree to which referable symptoms warrant treatment. What may be tolerable to one patient may prompt therapeutic intervention in another.

H&O What are some promising anti-CD20 RIT agents?

JM To date, 2 anti-CD20 RIT agents have been approved for commercial use in the United States: Y-90 ibritumomab tiuxetan (Zevalin, Spectrum Pharmaceuticals) and I-131 tositumomab (Bexxar, GlaxoSmithKline). Both agents can be administered in the outpatient setting. Toxicities are similar, with the exception of an approxi-

mate 10–20% rate of hypothyroidism associated with the I-131 conjugate in tositumomab. Infusion reactions may occur rarely, similar to those that can occur with rituximab (Rituxan, Genentech/Biogen Idec). The primary toxicity associated with RIT is prolonged myelosuppression, which typically lasts 6–8 weeks following infusion. Early reports raised concerns regarding the possible risk of treatment-related myelodysplastic syndrome (MDS) and acute myeloid leukemia. However, subsequent data analysis has not shown a statistically significant increase in either diagnosis among patients receiving RIT. To date, no randomized studies comparing ibritumomab tiuxetan and tositumomab have been completed.

H&O What encouraging studies involving ibritumomab tiuxetan in FL were presented at the 2011 Annual Meeting of the American Society of Hematology (ASH)?

JM Fowler and associates presented data surrounding the use of ibritumomab tiuxetan and rituximab maintenance following treatment with R-FND (rituximab, fludarabine, mitoxantrone, and dexamethasone) in the frontline setting. Thirty-six of 46 evaluable patients received the full course of treatment, which consisted of 4 cycles of R-FND followed by RIT, and subsequent rituximab as a single infusion every 2 months for 1 year. All patients had stage III or IV disease, and the majority had bone marrow involvement, with elevated beta-2 microglobulin. Following R-FND, partial response (PR) and complete response (CR) rates were 13% and 87%, respectively. Following ibritumomab tiuxetan consolidation, the CR rate increased to 91%. At a median 50-month follow-up, the projected 5-year overall survival

(OS) and progression-free survival (PFS) rates were 93% and 74%, respectively. Toxicity was mainly hematologic, with an expected grade distribution; however, 3 instances of MDS were reported, with 1 patient not receiving RIT. This trial addresses the concerns from previous studies demonstrating that high PR to CR conversions with RIT consolidation may have been a reflection of induction chemotherapy, not including rituximab. This trial addresses the concerns arising from previous trials in which high PR to CR conversion rates may have been the result of rituximab not being included in the induction chemotherapeutic regimen. This study demonstrated encouraging CR conversion rates in a high-risk patient population, despite rituximab being administered upfront. Arguably more impressive are the projected OS and PFS rates, and further follow-up is necessary to assess the durability of these results. Finally, the incidence of MDS is a concern, and while it is unclear whether this is a reflection of chemotherapy, RIT, or the combination, this approach may be most appropriate for those patients with high-risk disease, in whom standard therapy is unlikely to produce acceptable results.

In a study by Pica and colleagues, ibritumomab tiuxetan monotherapy in the frontline setting was evaluated. Fifty patients (of whom 48% had bone marrow involvement of less than 25% and 34% had high-risk FLIPI scores) received single-agent ibritumomab tiuxetan. There was an overall remission rate of 93% and a CR rate of 82%. Of the 26 patients who were polymerase chain reaction (PCR)-positive at the time of diagnosis, 77% converted to PCR-negative. The 2-year event-free survival (EFS) for all patients was 85%; additionally, 15 patients (55%) who were PCR-positive at diagnosis maintained their PCR-negative status. As expected, toxicity was primarily hematologic. The data presented in this cooperative group study are encouraging, and highlight the efficacy of frontline RIT as a viable approach. Further study is needed to identify those patients in whom frontline ibritumomab tiuxetan therapy is most appropriate.

Illidge and coworkers presented a study on the use of fractionated ibritumomab tiuxetan in patients with a significant burden of disease. Two reduced doses of therapy were administered in order to increase the total delivered radiation dose, which may in turn increase response rates and survival. Patients had untreated FL and at least 1 of the following criteria of high tumor burden: 1 lymphoma lesion greater than 7 cm or 3 separate nodes of 3 cm or more; symptomatic splenic enlargement; raised serum concentrations of either lactate dehydrogenase or beta-2 microglobulin; compressive syndrome; or the presence of B symptoms. Treatment consisted of 2 doses (11.1 MBq/kg) of ibritumomab tiuxetan, given 8–12 weeks apart. Patients with bone marrow involvement greater than 20% received 4 weekly infusions of rituximab (375 mg/m²) and

proceeded to fractionated RIT only if a repeat bone marrow biopsy demonstrated clearing of lymphoma with less than or equal to 20% involvement. Of 74 patients, 18% required rituximab pretreatment, and 76% completed the full treatment schedule. The second infusion of RIT was withheld secondary to hematologic toxicity (17%), human antimurine antibodies positive testing (5.6%), or other (1.4%). The overall response rate (ORR) was 97.1%. For the 17 patients who received only a single ibritumomab tiuxetan infusion, the ORR was 100%. At a median follow-up of 1.52 years, the PFS was 67%. The most common toxicity was hematologic, with expected rates and grade distribution after the first ibritumomab tiuxetan dose. After the second ibritumomab tiuxetan dose, related grade 3/4 hematologic adverse events increased to 36.4% for neutropenia (median duration, 31 days), 14% for anemia (8 of 55 patients required transfusion), and 56.4% for thrombocytopenia (median duration, 40 days). To date, there has been 1 case of MDS, diagnosed 26 months after treatment, and 1 death, due to metastatic breast cancer that was diagnosed 9 months after the last dose of ibritumomab tiuxetan. This study demonstrates the feasibility of sequential fractionated frontline ibritumomab tiuxetan therapy, which showed excellent response rates in this high-risk patient population. Follow-up will be important in order to assess the durability of this approach when compared with standard single-dose RIT.

H&O What other promising studies of RIT in FL were also presented at ASH 2011?

JM Several other important abstracts involving RIT in FL were presented at the 2011 ASH meeting. Follow-up data from a phase III randomized intergroup trial evaluating 6 cycles of CHOP plus rituximab versus 6 cycles of CHOP plus I-131 tositumomab in the frontline setting were reviewed. This study included 526 evaluable patients with bulky stage II–IV disease, and grade 1–3 histology. At a median follow-up of 4.9 years, 2-year estimated PFS in the R-CHOP and CHOP-tositumomab arms were both encouraging, at 76% and 80%, respectively. The 2-year estimated OS for the R-CHOP group was 97%, compared with 93% in the CHOP-tositumomab arm. While this study did not demonstrate improvement of CHOP-RIT versus R-CHOP, the 2-year OS and PFS were excellent in both arms, and statistical equivalence was demonstrated. Further analysis will be necessary to determine whether RIT can replace rituximab in the frontline setting, potentially as a means by which to retain rituximab efficacy in the relapsed setting.

A meta-analysis of RIT consolidation in previously untreated patients with FL was presented by Rose and associates. At least 1,136 records were reviewed; 8 studies met

inclusion criteria with 556 patients. A weighted average of 97.2% of patients had stage III/IV disease, and 73–98% of assessable patients had grade 1/2 disease. CR rates ranged from 51–97%, 2-year PFS ranged from 65–86%, and 5-year PFS ranged from 38–67%. The pooled estimates of the CR and OR rates following consolidative RIT were 78% and 98%, respectively. The 2-year and 5-year PFS estimates were 77% and 56%, respectively. In a cohort where the majority of patients have advanced disease, the estimated 5-year PFS rates from this meta-analysis are impressive. This study also demonstrates that consolidation with RIT following chemotherapy benefits untreated patients, with encouraging CR rates and 5-year PFS. When contrasting these data with results from the Eastern Cooperative Oncology Group ECOG 1496 study of maintenance rituximab after chemotherapy, RIT produces at least equivalent results in both 2-year PFS (77% vs 73.5%) and 5-year PFS (56% vs 46.4%). As suggested by the investigators, prospective comparative studies evaluating consolidative RIT with maintenance rituximab are warranted.

H&O What does the future hold for RIT in FL treatment?

JM Many questions remain surrounding the use of RIT in patients with FL. Optimization of treatment sequencing and induction regimens, the role of maintenance rituximab in patients who receive RIT, as well as the comparative data between maintenance rituximab and consolidation RIT, are all issues that will require further study. Among the many areas of ongoing RIT research, its potential use in the frontline setting is of particular interest. In 2005, a study by Kaminski and colleagues demonstrated very encouraging results with tositumomab in the frontline setting. While many of the patients in that study had limited burden of disease, by FLIPI, the vast majority of these patients were reasonable candidates for treatment. It could therefore be argued that the potential benefits of treating patients with RIT earlier in their disease course should continue to be thoroughly evaluated. While these and other questions remain, what is clear is that RIT represents a highly effective, and generally

well-tolerated, therapy in the relapsed, consolidation, and frontline settings. In my opinion, RIT remains a greatly underutilized treatment modality. I suspect that there are many reasons for this, including the logistics of treatment, patient anxiety regarding the use of therapeutic radiopharmaceutical agents, as well as the reliable response rates demonstrated by multiple chemotherapeutic regimens in both the frontline and relapsed settings. However, as the data for ibritumomab tiuxetan therapy continues to expand and strengthen, I expect its use will increase significantly. There have been dramatic advances in FL treatment over the past 10 years, and I anticipate continued progress in the years to come.

The impressive efficacy of ibritumomab tiuxetan illustrates the potential of the RIT concept. I anticipate this will remain an area of vigorous research, and will undoubtedly continue to advance the care of, and improve the outcomes for, patients with FL.

Suggested Readings

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