Users Fear that Lymphoma Drugs Will Disappear

By Ken Garber

Ill Rastetter, Ph.D., was brimming with optimism.

It was January 2003, and the Idec Pharmaceuticals CEO was touting his drug Zevalin (90 Y-labeled ibritumomab) at a San Francisco investors’ conference. The U.S. Food and Drug Administration had recently approved Zevalin for the treatment of relapsed non-Hodgkin lymphoma (NHL), the fifth most common cancer in the country. Initial Zevalin sales were low, but Rastetter expected the drug to take off just like another slow starter, rituximab, approved 5 years earlier.

“We will see the same pattern with Zevalin,” Rastetter said, “as this new technology is also tried and then adopted.”

But Rastetter was wrong. Over the last 4 years, sales of Zevalin, a radiolabeled antibody, improved little and are now declining. A second lymphoma radiopharmaceutical, Bexxar (131 I-labeled tositumomab), approved in June 2003, has sold even less than Zevalin. Last year Biogen Idec, as Zevalin’s owner is now known, announced its intent to divest the drug if a buyer could be found. And at the end of last year, according to several sources, the company discontinued Zevalin promotion and marketing efforts, although the drug continues to be available. (Biogen Idec would not comment on the reports.)

Biogen Idec’s recent actions, coupled with the anemic sales of both Zevalin and Bexxar, have placed the future of the young field of cancer radioimmunotherapy (RIT) in doubt. Rumors of the drugs’ possible future demise have even filtered down to lymphoma patients, some of whom are panicking.

“Patients are fit to be tied,” said Bexxar coinventor Mark Kaminski, M.D., a hematologist at the University of Michigan in Ann Arbor, who hears questions like these from his patients: “What if I need a retreatment?” and “What if somebody else in my family gets this disease? Or our friends?”

Kaminski even has patients in remission asking for Bexxar now, in case it’s unavailable later when they relapse and need it. Although Bexxar is not immediately threatened, its long-term availability is not guaranteed. “To have it disappear would be a tremendous loss for the patients,” Kaminski said.

If Zevalin and Bexxar were inferior treatments, their fate would hardly matter. But despite improvements in lymphoma therapy over the last decade—especially the introduction of rituximab—low-grade NHL is still considered incurable, and Zevalin and Bexxar show antitumor activity and less toxicity than some chemotherapy. Like rituximab, both drugs are antibodies targeting the CD20 antigen, present on relatively mature B cells. Unlike rituximab, they’re linked to radioactive isotopes—yttrium for Zevalin, iodine for Bexxar—to boost their cell-killing ability.

In clinical trials, Zevalin has produced overall response rates ranging from 74% to 82% in relapsed patients. In this latter group, the median response duration was 28 months. In a randomized trial comparing Zevalin to rituximab, 80% of Zevalin patients achieved an objective response, compared with 56% of rituximab patients, and twice as many patients achieved a complete response with Zevalin than with rituximab. In patients who relapsed after rituximab therapy, Bexxar has shown a 65% response rate, with 38% showing a complete response. The median duration of the response was 24.5 months in patients with a median of four prior chemotherapy courses.

Zevalin and Bexxar are “tremendously useful drugs,” said James Armitage, M.D., a hematologist at the University of Nebraska Medical Center in Omaha. “[They are] arguably the most active single agents in the treatment of follicular lymphoma.” (Follicular lymphoma is the main form of low-grade B-cell lymphoma.)

The main knock against RIT is that it hasn’t yet shown a survival advantage for patients—the ultimate standard for cancer therapy. “None of the studies have been powered with the numbers of patients to show a statistically significant survival advantage,” concedes Oliver Press, M.D., a hematologist and RIT researcher at the Fred Hutchinson Cancer Research Center in Seattle. “But of course it hasn’t been demonstrated for many of the other agents that have been widely used, either, such as fludarabine [and] bortezomib.” Large randomized clinical trials that should settle the survival question for RIT are under way.

NHL patients usually respond to initial treatment but inevitably relapse, with each remission progressively shorter, until death. In Bexxar’s pivotal trial, the median duration of response was 6.5 months after one Bexxar treatment, compared with 3.4 months after the last chemotherapy treatment. Complete responses in the same trial lasted a median of 47 months after Bexxar, compared with 6 months after their last chemotherapy. RIT patients “can have years of disease-free survival,” said Bruce Cheson, M.D., head of hematology at the Lombardi Cancer Center in Washington, D.C. “We haven’t seen that commonly with any other form of therapy.”

And the treatment is short, lasting about a week on an outpatient basis, and...
relatively nontoxic. The most common side effect is a temporary reduction in blood cell counts. For Bexxar, the drug’s gamma emissions require that precautions be taken to avoid exposing caregivers and family members to radiation, but it’s still an outpatient treatment.

“The delivery of [RIT] is actually, from a patient’s standpoint, the ideal therapy,” Thomas Witzig, M.D., a hematologist and Zevalin researcher at the Mayo Clinic in Rochester, Minn., wrote in an e-mail.

The Underuse Mystery
If these treatments are so great, why then are there poor sales? “One would predict that they would be wildly popular and that they would be used all the time,” Press said. Instead, he pointed out, “they are tremendously underused for their efficacy and safety profiles.” Cheson calls RIT “the most effective least-used treatment there has been in lymphoma.” Kaminski estimates that only 5%–10% of patients eligible for RIT are getting it.

Possible reasons include doctors’ discomfort with giving radioactive drugs, the fact that the drugs can’t be given to patients with cancer that has spread extensively to the bone marrow, concerns about causing secondary malignancies, and worries that using the drugs will preclude later treatments by destroying the marrow. But fewer than half of follicular lymphoma patients have clinically significant bone marrow involvement, and fears of high secondary malignancy risk and marrow destruction have so far not been borne out by clinical trial follow-up. In any case, all these reasons taken together do not come close to explaining the underuse mystery. The cost of RIT is not the reason, either; it’s no more expensive than chemotherapy plus rituximab, the current standard of care for newly diagnosed NHL patients.

One explanation is that RIT is far from ideal for the medical oncologists in private practice who make the treatment decisions. To give Zevalin and Bexxar, doctors must refer patients to radiation oncologists or nuclear medicine specialists (often in academic medical centers) and then coordinate treatment. This involves more effort than simply giving chemotherapy drugs or rituximab in clinic—and it means less money because the specialist gets the insurance company reimbursement not the medical oncologist. Even though medical oncologists give patients a nonradio-labeled antibody at the beginning of treatment, for dosimetry purposes, they may go unreimbursed unless they take advantage of certain arcane reimbursement codes.

So RIT, viewed from the standpoint of the medical oncologist’s convenience and financial compensation, has problems. “If you’re a busy practitioner and can give other good drugs, it is just plain easier,” Marshall Lichtman, M.D., executive vice president of research at the Leukemia and Lymphoma Society, wrote in an e-mail.

But what’s best for patients may be a different question. Kaminski contends that RIT is often superior to other lymphoma treatments. Chemotherapy can drag out for months with prolonged toxicity. “Unless we change our mindset about this, we’re going to continue to see a kind of whittling away of this [RIT] technology and perhaps even its disappearance,” he said.

Kaminski blames misinformation about RIT, in part, for the treatment’s poor acceptance. (Kaminski shares royalties from Bexxar sales and receives occasional honoraria and research funds for clinical studies from GlaxoSmithKline.) The Leukemia and Lymphoma Society’s Lichtman, for example, wrote in an e-mail that, for Bexxar, “patients have to be sequestered for about 48 hours, if they are excreting radioiodine,” and “there has not been observation of large numbers of patients for long-term [bone marrow] risks.”

No isolation is required, Kaminski pointed out, just simple precautions at home—mainly sleeping in a separate bed and using a separate bathroom, if possible. As for long-term safety data for Zevalin and Bexxar, experts can differ as to how much follow-up is necessary. But “published data would suggest they’re no more leukemogenic than other leukemogenic therapies we use all the time, like alkylating agents,” Armitage said. The notion that RIT burns out the bone marrow “is absolutely not correct,” Kaminksi said, unless prior chemotherapy already has inflicted irreparable damage. While occasional patients do develop myelodysplastic syndrome or leukemia, “the risk is not much if any higher than giving more cytotoxic chemotherapy,” Cheson said.

Running Out of Time?
A big problem, Kaminski added, is that so few centers have even tried RIT. Once people have seen that this is accomplishable, and relatively straightforward, he said, they’re often convinced. “But it takes a threshold [of experience] to be met.”

Ongoing clinical trials may eventually help, specifically a large NIH-funded multicenter trial comparing chemotherapy and rituximab to chemotherapy and Bexxar in patients with newly diagnosed follicular lymphoma. If favorable to Bexxar, “it could change the way we do business,” Armitage said. A similar trial is under way for Zevalin. The Bexxar study should meet its goal of continued on page 501
treating 500 patients by the end of the year, with survival data available perhaps by late 2009. “It’s going to be a while, unfortunately,” said Press, the trial’s coordinator. And a long-term survival benefit may take even longer to become apparent.

In the meantime, doctors and patients are watching Zevalin and Bexxar to see what their sponsor companies do. In December GlaxoSmithKline, Bexxar’s owner, entered into a codevelopment agreement with Genmab in Copenhagen, Denmark, to develop ofatumumab, a non-radiolabeled anti-CD20 antibody. Some patients worry that GlaxoSmithKline could eventually shelve Bexxar in favor of the simpler and potentially more lucrative ofatumumab. “The community has been slow to adopt [RIT], and we are continuing to study Bexxar and assess opportunities for the product,” GlaxoSmithKline spokesperson Sarah Alspach said. As for Zevalin, “Biogen Idec has no plans to take Zevalin off the market at this time,” a company representative said in an e-mail.

But only higher sales will ultimately persuade Biogen Idec and GlaxoSmithKline to continue providing these drugs. Kaminski proposes rearranging the reimbursement scheme to get more money to medical oncologists and suggests loosening licensure requirements so they can give radiopharmaceuticals. Ultimately, “it’s got to be patient driven, somehow,” he said. “By alerting the world out there at large, and patients out there at large, there may become more of a [movement] for reigniting a flame under this treatment.”

“To have [RIT] disappear would be a tremendous loss for the patients,” Kaminski added. “We’ve never seen remissions this durable, with any other product, with any other single agent, as we have with radioimmunotherapeutic products.” Kaminski even thinks that Zevalin and Bexxar, if used early enough in treatment, could cure low-grade NHL—a bold (and so far unproven) statement.