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## Market Forces Cited in Lymphoma Drugs' Disuse

By [ALEX BERENSON](#)

The patients' stories sound nearly impossible.

After an hourlong infusion, Linda Stephens, 58, has been [cancer](#)-free for seven years. Dan Wheeler, three years. Betsy de Parry, five years. Before treatment, all three had late-stage non-[Hodgkin's](#) lymphoma, a cancer of the immune system, and a grim prognosis.

All three recovered after a single dose of Bexxar or Zevalin, both federally approved drugs for lymphoma. And all three can count themselves as lucky.

Not just because their cancers responded so well. But because they got the treatment at all.

Non-Hodgkin's lymphoma is the fifth most common cancer in the United States, with 60,000 new cases and almost 20,000 deaths a year. But fewer than 2,000 patients received Bexxar or Zevalin last year, only about 10 percent of those who are suitable candidates for the drugs.

"Both Zevalin and Bexxar are very good products," said Dr. Oliver W. Press, a professor at the [University of Washington](#) and chairman of the scientific advisory board of the Lymphoma Research Foundation. "It is astounding and disappointing" that they are used so little. The reasons that more patients don't get these drugs reflect the market-driven forces that can distort medical decisions, Dr. Press and other experts on lymphoma treatment say. A result can be high costs but not necessarily the best care.

The drugs have not been clinically proven to prolong survival, compared with other therapies. But patients are more likely to respond to them than standard treatments, and trials to test whether the drugs do have a survival benefit are nearly complete.

Other, more thoroughly tested lymphoma drugs are preferred as first-line treatments. But doctors often repeatedly prescribe such drugs even after they have lost their effectiveness — and when Bexxar and Zevalin might work better.

One reason is that cancer doctors, or oncologists, have financial incentives to use drugs other than Bexxar and Zevalin, which they are not paid to administer. In addition, using either drug usually requires oncologists to coordinate treatment with academic hospitals, whom the doctors may view as competitors.

As a result, many doctors prescribe Bexxar and Zevalin only as a last resort, when they are unlikely to succeed because the cancer has advanced. "Oncologists use everything in their cupboard before they refer," Dr. Press said. "At least half the patients who get referred to me have had at least 10 courses of treatment."

While Bexxar and Zevalin help many patients, only a minority become cancer-free for many years. But clinical trials indicate that they are as good as or better than other treatments. When the drugs were approved, analysts expected they would be used widely.

But the drugs have run into an obstacle that so far has been impassable. Because they are radioactive, they are almost always administered in hospitals, not doctors' offices. As a result, doctors are not paid by Medicare and private insurers for prescribing them, as they are when they give patients a more common treatment, [chemotherapy](#).

In addition, most oncologists outside academic hospitals treat many different cancers and may be only vaguely familiar with the drugs, said Dr. Andrew D. Zelenetz, chief of the lymphoma service at [Memorial Sloan-Kettering Cancer Center](#). "There are a number of barriers," Dr. Zelenetz said.

Dr. Press and Dr. Zelenetz acknowledge that they have their own financial incentives to support the drugs. Dr. Press has been paid to speak at medical education seminars sponsored by the makers of the drugs. Dr. Zelenetz has been paid when the companies sponsor clinical trials at Memorial Sloan-Kettering. But both said the money was a small part of their total income and had not colored their views.

Some patients say they would not have received Bexxar and Zevalin if they had not demanded them. Mr. Wheeler of Kalamazoo, Mich., said he received Bexxar in April 2004 only after insisting on it when his lymphoma recurred. "I told my local oncologist, I want Bexxar, you give me a referral," Mr. Wheeler said. "I've been a real pain."

Mr. Wheeler, whose lymphoma was diagnosed in 2000 and recurred in 2003, has been cancer-free since receiving Bexxar. His cancer was growing when he received the infusion. He thinks he would be dead by now if he had not received the drug.

Ms. Stephens feels similarly. She was diagnosed with lymphoma in December 1998, and chemotherapy proved both difficult and ineffective. By August 1999, her disease was spreading. "Every lymph node in my body was involved," she said. She received Bexxar as part of a clinical trial in January 2000 and quickly began gaining strength. She has remained in remission since, she said.

Zevalin and Bexxar are the first in a new class of drugs called radioimmunotherapies. Essentially, they deliver radioactive particles directly to cancerous cells to kill them. Idec, now part of Biogen Idec, invented Zevalin. Corixa, a Seattle company bought by [GlaxoSmithKline](#), developed Bexxar. Both drugs are very expensive, costing about \$25,000 per treatment. But one dose is usually enough. The cost of the drugs is similar to a full four-month regimen of chemotherapy and Rituxan, another lymphoma treatment.

For decades, lymphoma has been treated with chemotherapy, drugs that attack cancer cells but that can have severe side effects. Alongside chemotherapy, most patients now get Rituxan. It was discovered by Idec, the same company that found Zevalin, and is marketed in the United States by [Genentech](#).

The [Food and Drug Administration](#) approved Rituxan in 1997. Since then, the drug has become standard treatment for newly diagnosed lymphoma patients, based on clinical trials showing that it makes chemotherapy more effective.

Because lymphoma is relatively common, and Rituxan costs \$20,000 for a typical course of treatment, it is the top-selling cancer drug worldwide, with sales in 2006 of \$4 billion.

Doctors agree that Rituxan is an excellent drug with only minor side effects for most patients.

Still, the few head-to-head clinical trials that have been conducted show that Bexxar and Zevalin are as effective as Rituxan, if not better.

In a study published in *The Journal of Clinical Oncology* in 2002, the [tumors](#) in 80 percent of patients who received chemotherapy and Zevalin shrank, compared with 56 percent who received chemotherapy and Rituxan. Of patients who received Zevalin, 30 percent went into complete remission, compared with 16 percent who got Rituxan.

Dr. Antonio J. Grillo-López, who oversaw the development of Rituxan and Zevalin as the chief medical officer at Idec, thinks Zevalin is the more potent of the two. "The early-stage studies showed that in fact Zevalin was superior," he said. Dr. Grillo-López retired from Idec in 2001 and said he no longer had any financial interest in either drug.

When it reviewed the clinical trials for Zevalin in 2001, the F.D.A. found that "as compared to the Rituxan therapy, Zevalin was associated with a superior overall response rate." The F.D.A. noted that another study found that 58 percent of people who had failed Rituxan treatment showed some response to Zevalin. Bexxar has shown similar results.

The F.D.A. approved Zevalin in 2002 and Bexxar in 2003, in both cases for the treatment of slow-growing lymphoma that had failed previous treatments.

When regulators approved Zevalin, Wall Street analysts projected it would reach \$100 million in sales in 2003. [Merrill Lynch](#) predicted it could eventually hit \$500 million in sales — about 20,000 doses a year.

But Zevalin hit roadblocks immediately. Its five-figure price caused insurers to balk. Further, its radioactivity made some oncologists worry that it might prevent them from giving other treatments later.

Prescribing Zevalin also requires oncologists to coordinate care with the hospitals that administer it. To get either Zevalin or Bexxar, patients first receive a low-[radiation](#) diagnostic dose, then imaging scans, then a high-radiation therapeutic dose, which comes a week after the first dose. Over the next weeks the patient's red and white blood cell counts must be monitored.

The back-and-forth makes the treatment complicated to oversee, said Dr. Joseph M. Connors, a lymphoma specialist in Vancouver, British Columbia. "The doctors looking after people tend to turn to tools that they themselves know how to use and are familiar with," he said.

For most oncologists, infusions of chemotherapy, Rituxan and other drugs are still their primary source of income. Even so, oncologists might have felt bound to use Bexxar and Zevalin if the drugs had been proven to extend survival over older treatments, Dr. Connors said. While preapproval trials showed that the drugs shrank tumors more frequently than Rituxan and suggested patients would survive longer, the test groups

were too small to prove it.

Dr. Connors said that Idec and Corixa should have designed their clinical trials to prove — not just suggest — that the drugs increased survival.

Two clinical trials meant to answer that question are under way, but their results have not been reported. Until they are, doctors will be reluctant to use Bexxar and Zevalin, Dr. Connors said. For now, the drugs remain niche products. Biogen Idec reported worldwide sales of \$18 million for Zevalin last year. That was about 1,000 doses of Zevalin used commercially. Dr. Press reported that GlaxoSmithKline had sold about 600 doses of Bexxar last year.

Advocates for the drugs worry the companies may stop making them. Biogen Idec said in October that it might shed Zevalin. Although the company continues to manufacture the drug, it no longer actively promotes it. A spokeswoman for Biogen Idec said the company planned to keep making Zevalin and continued to offer technical support to doctors using it. GlaxoSmithKline said it expected to keep making Bexxar.

Patients who have benefited from Bexxar and Zevalin say they cannot understand why the drugs are not more widely used.

Ms. de Parry received Zevalin in 2002, when she was 52. She had already failed chemotherapy and Rituxan. But she responded quickly to the injection and has remained cancer-free. "It's not that I believe that radioimmunotherapy is right for everybody," she said. "I just think that patients, all patients, should know their options."

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