

FEATURE STORY

Trying Something New

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Long-standing treatments for non-Hodgkin lymphoma have something new to offer.

Most patients in the midst of treatment for non-Hodgkin lymphoma, commonly referred to as NHL, would laugh at the thought of one day competing in an Ironman triathlon. But for Adam Schoener of Birmingham, Michigan, that laughable thought turned into reality last June. “I never did triathlons before I got sick,” he says. “But it’s a great way to gain back some control in your life.” Raising money along the way for The Leukemia and Lymphoma Society (LLS) was just a side benefit.

Schoener was diagnosed in 2004 at age 35 with a fast-growing type of NHL called diffuse large B-cell lymphoma. As often occurs, Schoener’s diagnosis came without warning, just weeks after an annual physical found him in ideal health. “At first I just thought it was heartburn,” he recalls. “But soon I couldn’t catch my breath. That’s when my wife took me to the ER.” Imaging scans and biopsies revealed a Twinkie-size mass pressing on his heart and lungs.

Now, more than four years after his diagnosis, Schoener is cancer-free. His story is just one indication of the strides being made in the treatment of NHL, which affects approximately 66,000 Americans and 300,000 people worldwide each year. Treatment can be challenging, in part because NHL is a collection of nearly 60 related diseases, according to LLS, which differ in biology, treatment, and prognoses.



Barbara Barrow's slow-growing lymphoma was monitored with regular CT scans. Photo by David Hollingsworth.

"NHL is really a complex problem," says Andrew Zelenetz, MD, chief of the Lymphoma Service at Memorial Sloan-Kettering Cancer Center in New York. "It's critical to realize that this is not just one disease we are dealing with."

Lymphomas, non-Hodgkin and Hodgkin alike, originate in the lymph system, a fluid network that carries immune cells throughout the body. The uncontrolled division of normally protective white blood cells causes NHL, leading to tumors in the lymph nodes that can spread to other parts of the body.

NHL can be sneaky, sharing early signs of the flu—fever, nausea, and fatigue. For Barbara Barrow, a 65-year-old real estate agent diagnosed in 2002 with early-stage follicular lymphoma, a slow-growing variety, the only warning sign was swollen lymph nodes. Barrow's doctor suggested a "watch and wait" approach with regular CT scans after her first few scans showed the cancer was growing very slowly.

Slow growth may be good news with some cancers, such as breast or colon, but that's not always the case with NHL. Although somewhat counterintuitive, the fast-growing "aggressive" forms of NHL are more easily cured, if treated early, than the slow-growing "indolent" varieties.

"It's not a paradox when you think about how [chemo] drugs work, which is to target growing, dividing cells," says Bart Kamen, MD, PhD, chief medical officer of LLS and former director of pediatric hematology and oncology at the Cancer Institute of New Jersey. "If the disease is growing rapidly, we can kill it quickly as long as it doesn't get the patient first."

Attacking Aggression

Schoener's and Barrow's cancers—diffuse large B-cell lymphoma and follicular lymphoma—are the two most common varieties of NHL, accounting for about 75 percent of adult NHL cases. Both diseases arise in a type of immune cell, called B cells, which produce antibodies that help protect the body from infection.

For decades, the standard treatment regimen for aggressive forms of NHL was intravenous infusion with a chemotherapy cocktail known as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), which cured approximately 30 percent of patients with diffuse large B-cell lymphoma. More recently, the efficacy of CHOP dramatically improved after studies showed combining CHOP with an immunotherapy drug called Rituxan (rituximab) increased the number of patients who had complete disappearance of disease. Of patients receiving R-CHOP, 76 percent achieved a complete response compared with 64 percent on CHOP alone, according to one study. A separate study found that adding Rituxan to CHOP also boosted three-year overall survival rates from 84 percent to 93 percent.

Rituxan, which received its first approval for lymphoma from the Food and Drug Administration more than a decade ago, works by targeting the CD20 protein that is found at high levels on cancerous B cells. R-CHOP has been successful in treating aggressive forms of NHL and is now the standard first-line therapy for these diseases.

Patients typically receive six to eight cycles of R-CHOP at three-week intervals, although some oncologists advocate a more accelerated two-week regimen. Schoener's schedule fell in between—he received eight rounds of R-CHOP at two-and-a-half-week intervals followed by radiation therapy. The optimal dose and schedule of R-CHOP remains a matter of debate and is currently being tested in clinical trials.

Despite the success of R-CHOP, approximately 40 to 50 percent of patients with aggressive NHL relapse after the initial treatment, pointing to a need for new options. High-dose chemotherapy followed by autologous stem cell transplantation is only appropriate for select patients, as many are too frail for this grueling treatment.

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To help prevent relapse, some oncologists recommend continued treatment with Rituxan—known as maintenance therapy—after initial success with R-CHOP. “Maintenance may be killing tumor cells we can't see,” says proponent Kamen. “It's a way to turn cancer into a chronic disease—one that can be managed.”

Because it's still unclear whether maintenance improves overall survival, other physicians are holding off on recommending maintenance. However, a new report, published in the February 18 issue of the *Journal of the National Cancer Institute*, examined data from five randomized trials looking at maintenance Rituxan therapy compared with observation or treatment at relapse in follicular lymphoma. The analysis, which contained nearly 1,000 patients, found a 40 percent improvement in overall survival in patients who received maintenance

Rituxan. Although studies indicate that patients can be safely treated with Rituxan for up to two years, longer follow-up is needed to determine whether continual treatment carries health risks.

“I’m willing to wait to see what the data show,” says skeptic Zelenetz. Results of the eagerly awaited PRIMA trial, which examined the effects of Rituxan maintenance in more than 1,200 follicular lymphoma patients, are expected within a year or two.

Stifling Stealth

Patients with indolent (slow-growing) forms of the disease still await a success story equivalent to that of R-CHOP for aggressive NHL.

“Those (indolent) diseases are typically not curable,” says Owen O’Connor, MD, PhD, of the Herbert Irving Comprehensive Cancer Center at Columbia University, “and the goals of care are focused on chronic management with less toxicity and good disease control without significantly compromising quality of life.”

No general consensus exists about the best way to tackle indolent disease at the outset. R-CHOP, the most commonly used therapy, has proven to have some success. In one study, more than 40 percent of patients remained disease-free for nearly 10 years after treatment. But since cancer cells in these patients are not rapidly dividing, the cells often escape the regimen’s deadly effects. And because the anthracycline component of the CHOP mixture can increase the risk of heart damage, patients are typically treated with only one course of R-CHOP, and thus run the risk of losing this option down the road if their disease transforms into aggressive NHL, which occurs in 3 percent of patients each year. “I like to keep that one in my back pocket,” says Zelenetz.

Zelenetz, like many oncologists, prefers to start with the watch-and-wait approach for indolent disease as long as symptoms are still mild. Those in favor of this approach believe treatment should begin only when disease symptoms arise or the cancer progresses, but others question whether the delay is appropriate.

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“I believe observation still has a role in lymphoma,” says Zelenetz. “Others will disagree with me. Some people say we should use rituximab because we have it, and it has low toxicity.” Again, Zelenetz says he awaits proof from clinical research before jumping on that bandwagon; an ongoing clinical trial is comparing watch-and-wait to immediate treatment with Rituxan.

Barrow’s physician initially opted for observation over immediate treatment for

her slow-growing lymphoma, but then failed to recognize the flu-like symptoms and achy legs she developed two years later as symptoms of cancer progression. Barrow opted for a second opinion, and her new oncologist found her cancer had started picking up speed and had spread to her bone marrow. She was put on R-CHOP.

“I had my first treatment on a Thursday, and by -Saturday, there were no visible [cancerous] lymph nodes left. They had just melted away,” says Barrow.

Barrow only briefly suffered from some of the typical side effects of R-CHOP—fever, chills, and nausea—and her cancer disappeared after three rounds of treatment.

A newly approved option is Treanda (bendamustine). Although the agent has been used for decades in Europe to treat solid tumors and lymphomas, it was just approved by the Food and Drug Administration in late 2008 for indolent B-cell NHL. (The FDA approved Treanda for chronic lymphocytic leukemia in early 2008.)

The approval was based on a single-arm study of 100 patients, 17 of whom had a complete response to the drug, meaning no signs or symptoms of the disease were present. Side effects of Treanda may include nausea, vomiting, anemia, and fatigue.

Improving On What's Known

Based on the success of Rituxan, researchers have designed related antibody-based drugs, some of which have been approved for treating relapsed indolent lymphomas or those that did not respond to prior treatments.

One twist is to combine these drugs with the deadly effects of radiation therapy by attaching a radioactive molecule directly to the drug. The modified drug can then deliver a lethal dose of DNA-damaging radiation directly to the tumor cells. Radioactive antibody-based therapies approved for the treatment of low-grade NHL include Bexxar (tositumomab) and Zevalin (ibritumomab tiuxetan).

In a recent study of 51 patients with refractory B-cell lymphoma, 37 patients responded to Zevalin, with nine of those 37 having a long-lasting response of more than three years. Other research showed that a third of patients with Rituxan-resistant disease went into complete remission after treatment with Bexxar.

Certain drawbacks, however, make radioactive therapies less popular than some might hope. Part of the problem is their high price. And giving patients radioactive drugs is risky and requires the close supervision of a radiologist.

“I personally think that they’re underused,” says Kamen. Bruce Cheson, MD, head of hematology and director of hematology research at Lombardi Comprehensive Cancer Center at Georgetown University, agrees. “They’re the most effective but least used drugs for lymphoma,” says Cheson.

Another relative of Rituxan called ofatumumab (the proposed trade name is Arzerra) may be just as effective as Rituxan with less toxicity. Not yet approved

for treating NHL, the increased benefit of ofatumumab is thought to be due in part to its ability to bind to the protein CD20 with increased affinity.

Yet other antibody-based drugs hone in on different proteins on the cancer cell. Campath (alemtuzumab), for instance, targets a protein called CD52 instead of CD20 and is now in early-phase trials for NHL. Already approved for a type of leukemia, Campath may also work in NHL since CD52 is found on a wide variety of immune cells. Campath, however, is so adept at destroying its target cells that the immune system can be dangerously dampened, leaving the patient susceptible to sometimes life-threatening infections.

[View Illustration: Killer Pathways](#)

Coming Down the Pipeline

For patients who have exhausted other options, many clinical trials are available. “Right now, we’re living in the most exciting time ever in the history of cancer care,” says O’Connor. “There are enormous numbers of new drugs that are beginning to emerge that offer you a chance to reduce the non-specific effects of chemotherapy and, theoretically, gain better efficacy.”

One promising option for NHL is Revlimid (lenalidomide), an agent approved to treat multiple myeloma and myelodysplastic syndromes. Scientists are still investigating how the drug works against lymphoma, but one effect is to ramp up the activity of immune cells that attack and kill tumor cells.

Another drug undergoing clinical testing is pralatrexate, which O’Connor helped develop. The agent shuts down multiple metabolic pathways that cells need to survive, but the trick with pralatrexate, explains O’Connor, is in its specificity.

“Pralatrexate is uniquely designed to be selectively transported into cancer cells over normal cells.” It is proving particularly successful in less common forms of NHL that stem from T cells rather than B cells, and O’Connor hopes it will be approved for peripheral T-cell lymphoma in the coming year.

Another treatment showing potential is a class of drugs known as histone deacetylase inhibitors. The first of this class was Zolinza (vorinostat), approved in 2006 for T-cell lymphoma. Zolinza and related therapies work by reactivating genes that may have been inappropriately shut down by cancer. The re-ignition of these genes helps control normal cell growth and development. (Read more about these agents in [“Medicine’s New Epicenter? Epigenetics”](#) from the Winter 2008 issue.)

With a plethora of drugs working their way through clinical trials, choosing the best trial for each patient can be challenging. “With 60 different kinds of lymphomas, wouldn’t it be great to say that we have one drug that kills all lymphomas?” says O’Connor. “But it’s not going to emerge that there is one drug that is the panacea for all forms of NHL.” Instead, he hopes a better understanding of the biology of each type of NHL will eventually allow physicians to use tailored, or individualized, combinations of targeted drugs along with

conventional chemo-therapy to most effectively treat each patient's disease.