Indolent Lymphoma: Can Rituximab Resolve the Watch-and-Wait Debate?

By Emma Ross

For the past 30 years, lymphoma experts have debated how to manage patients with indolent lymphoma who have a low tumor burden and no symptoms. Because most of them will need therapy eventually, should oncologists blast the disease with every regimen they can think of in a bid to cure or get it under control as soon as possible, even though there’s no evidence this improves survival? Or should they spare patients the toxic effects and simply observe the slow-growing disease until therapy is really needed? The debate reignites every time a promising new treatment emerges.

It has become particularly vigorous over the last few years with the advent of biological therapies such as the monoclonal antibody rituximab (Rituxan), which provides longer-lasting remission with fewer side effects than chemotherapy. Data emerging in the last 3 years show that rituximab also improves survival in symptomatic follicular lymphoma—something that chemotherapy alone has not achieved. This finding has some holdouts wondering whether it might finally be time to abandon watch-and-wait for patients with less-threatening disease.

The topic was the subject of a debate session at the meeting of the European Society of Medical Oncology in Berlin in late September 2009. Although watch and wait was a clear winner among the 200-strong audience, with almost nobody raising a hand in favor of early treatment at the close, experts say the debate is very much alive in the wider field in both the United States and Europe.

“When you have a disease where you can sit down and discuss with the patient, in the same conversation, anything from watch and wait to oral chemotherapy, intravenous chemotherapy with immunotherapy, radioimmunotherapy, and autologous bone marrow transplant, you know we don’t understand what the right answer is,” said Samuel Silver, M.D., Ph.D., a hematologist at the University of Michigan in Ann Arbor.

About 40% of all non-Hodgkin lymphomas are indolent, with follicular lymphoma being by far the most common. Experts estimate that about one-third of those patients would be candidates for watch and wait because of a low tumor burden or absence of symptoms or other factors requiring immediate treatment. Most will eventually need treatment for this generally incurable disease, usually within 2–3 years, but a small proportion, perhaps 10%–20%, can go 10 years or more without therapy. The problem is that there’s no way to identify which patients can safely be spared unnecessary treatment.

Until the late 1970s, immediate chemotherapy was standard, but thinking started to shift after a 1979 retrospective trial showed no difference in survival between immediate and delayed chemotherapy. Three randomized trials followed in the 1980s and 1990s, confirming no overall survival benefit from immediate chemotherapy, and from then on medical students and oncologists were taught that indolent lymphoma should be initially managed with watch and wait.

“If you start treating immediately or delay it, the duration of life is the same. What changes is if you are in remission or not, but that doesn’t matter if you don’t have symptoms,” said Michele Ghelmini, M.D., head of oncology at the Oncology Institute of Southern Switzerland in Bellinzona. “So if you have a patient who has the disease but doesn’t notice he has it, why not let him live quietly until he has symptoms?”

No Consensus in Practice

But not everyone has followed that line. For instance, American physicians are thought to be more likely than their European counterparts to opt for early treatment, even though watch and wait is standard practice in both places.

“There are many physicians and very smart lymphoma investigators who treat everybody at the get-go, and it just proves that there’s no consensus,” said Brad Kahl, M.D., director of the lymphoma service at the University of Wisconsin in Madison. “I think in the U.S., a low-tumor-burden, asymptomatic patient is more likely to start on treatment right away than someone in Europe, but it totally depends on the patient and who their doctor is.”

One reason for the variation in practice might be that even physicians who agree watchful waiting is best disagree on the criteria. For instance, the definition of “symptomatic” is vague, and some hematologists don’t believe that symptom status should even be in the decision mix. Some use risk scores to help them decide, whereas others think that’s inappropriate.

Despite differences of opinion, experts seem to agree that rituximab has changed the game dramatically.

“Ten years ago I was very dogmatic that we don’t need early treatment, but nowadays I do see it in a more differential way,” said Martin Dreyling, M.D., Ph.D., professor of medicine at University of Munich Hospital in Germany. “If the patient is a little bit more tired than normal or there are some lymph nodes they don’t like in their neck, in rare cases we do treat these patients,” he said. “But I only use biologicals [such as rituximab].”

However, adding rituximab to the armory has not moved all clinicians in the same direction. Whereas it has made many doctors more open to the idea of immediate therapy, it has made Fredrick Hagemeister, M.D., a convert to watch and wait.

Hagemeister, a professor of medicine at the University of Texas M. D. Anderson Cancer Center in Houston, said he used to believe strongly in immediate treatment. But he now believes that with rituximab, he can afford to
watch and wait without compromising results. His new attitude comes from his experience combining rituximab with the CHOP chemotherapy regimen (cyclophosphamide, hydroxydaunorubicin, vincristine [Oncovin], and prednisone), which is known as R-CHOP.

"After R-CHOP, when the disease relapses, it comes back very indolent. It used to be a bad disease on relapse, but I think rituximab must be doing something to alter the natural history of the disease," he said. "We are basically not treating patients [with limited disease] immediately any longer, and we were one of the last holdouts."

Point–Counterpoint
The case for watching and waiting is strong, experts say, mostly because some patients don’t need therapy for a long time and there’s no evidence that early treatment provides better overall survival than delayed treatment.

During the Berlin debate, Ghielmini outlined some arguments that proponents of early treatment tend to make and refuted each in turn. One is that waiting may allow tumor growth to cause irreversible organ damage. But the tumor grows so slowly that treatment can be initiated before organs are threatened, Ghielmini countered.

Fears also exist that waiting increases the risk of resistance to rituximab. Ghielmini cited studies showing no difference between the amount of disease and the response rate, which he said confirms that the disease doesn’t become more resistant while growing. In fact, say proponents of watch and wait, early treatment may increase the risk of resistance, blunting the drug’s power when it’s really needed later in the course of the disease.

The risk of tumor transformation is another argument in favor of treatment. However, although transformation from indolent to a more aggressive cancer is a real risk, research shows no difference in the incidence of transformation between patients who receive immediate treatment and those on watch and wait, Ghielmini said.

However, even proponents of watch and wait acknowledge some good arguments for early treatment. For instance, surveillance may be difficult for some patients, because they either live far away from a center or have trouble with compliance. Also, some physicians believe that with early treatment, they may be able to give patients a considerable amount of time off treatment by getting the disease under control early.

The strongest argument, some say, is patient demand. Some patients cannot accept the idea of no treatment, knowing that they have a malignant disease. And now that there are less-toxic alternatives to chemotherapy, immediate treatment looks more feasible, if only as a way to relieve the psychological stress. Oncologists on both sides of the question are awaiting the results of two major trials testing the drug in patients who would be candidates for watch and wait outside the trial.

Will Trials Resolve?
The first trial, headed by David Linch, MB BChir, in the UK, is testing whether giving immediate rather than delayed rituximab spares people chemotherapy for long enough to make the approach worthwhile. One arm involves watching and waiting until symptoms occur or the disease progresses to the point of needing treatment, whereas the other involves immediate rituximab, followed by 2 years of rituximab maintenance therapy. The primary endpoint, which should be reportable around mid 2011, is time to requiring alternative therapy—mainly chemotherapy. Progression-free survival and overall survival are secondary endpoints.

The second trial, called RESORT, is a U.S. study that Kahl is running. It involves initial rituximab followed by either maintenance rituximab therapy indefinitely or observation until rituximab retreatment is needed.

“If the Linch study shows an overall survival advantage for treating with [rituximab] right away, I think everybody would drop watch and wait overnight,” Kahl predicted.

Dreyling agreed, adding that the trial could be pivotal even before the full results are known. “We won’t be able to wait for the results on overall survival, which might take another 10 years or so, but if progression-free survival moves to, say, 5 years, then watch and wait will no longer be in the driver’s seat,” he said. “Similarly, if the RESORT trial comes up with median progression-free survival in the range of 5 or more years, then the majority will forget about watch and wait.”

However, Linch himself is not sure that the results of his trial will convince everyone. “There will still be controversy, whatever this trial shows, about how to manage younger patients,” said Linch, who is the director of the Cancer Research UK Cancer Centre at University College London. “For those people who believe you have to strive for a cure, even though you’ve got no data to say you can achieve it, they will want to give chemotherapy and rituximab straight away. For them, the question will not be watch and wait versus rituximab, but rituximab versus rituximab plus chemotherapy. This trial won’t solve that because it’s not testing that question.”

The definitive way to settle the debate, several experts say, would be to come up with reliable biomarkers. “I think we need to work hard to come up with prognostic systems that allow us to precisely and confidently predict which patients are likely never to suffer from their disease, and those are the patients we should not treat,” said Brian Link, M.D., at the University of Iowa in Iowa City. Research in that area is ongoing.

Dr. Hagemeister has served as consultant for several companies, including Genentech, which markets rituximab in the U.S. Dr. Dreyling is a member of the scientific advisory board of Roche, which markets rituximab in Canada and Europe; he has also received research support and a speaker’s honorarium from Roche. Dr. Linch has served as a consultant to Roche.