

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Rituximab Maintenance in Follicular Lymphoma



Paul M. Barr, MD
Assistant Professor
Department of Medicine
University of Rochester Medical Center
Rochester, New York

H&O What is rituximab's mechanism of action?

PB Rituximab (Rituxan, Genentech/Biogen Idec) is a chimeric antibody against CD20. We do not fully understand the mechanisms responsible for its antitumor effects, but direct signaling, complement-dependent cytotoxicity, and antibody-dependent cellular cytotoxicity (ADCC) all appear to play some role in rituximab's efficacy, with ADCC likely playing the most prominent role in follicular lymphoma.

H&O What is the current prognosis for follicular lymphoma?

PB A group from Stanford University has collected data on follicular lymphoma for more than 50 years, and their results demonstrate how prognosis has changed over time. Data from their retrospective analysis, published by Tan and colleagues, suggest that overall survival (OS) for follicular lymphoma has improved dramatically, especially in the past 2 decades. They divided the data set into 4 eras based on treatments: 1960 to 1975, 1976 to 1986, 1987 to 1996, and 1997 to 2003.

Many things certainly changed over those 4 decades, but the most important conclusion is that the median OS has increased from 11 years in the first 2 eras to approximately 18 years in the last 2 eras. In eras 3 and 4, we saw advances like purine analogues and stem cell transplantation, but probably the most notable change in treatment is the use of anti-CD20 therapy, especially rituximab. There is no doubt that improvement in OS has at least in part resulted from increased use of rituximab.

H&O Could you describe the studies in which rituximab maintenance was associated with a benefit in OS?

PB There are, overall, at least 10 randomized studies testing maintenance rituximab in indolent and follicular lymphoma in various settings and populations. There is a lot of variability among the different studies, but most of them have demonstrated an improved progression-free survival (PFS) without an improvement in OS.

The European Organisation for Research and Treatment of Cancer (EORTC) 20981 trial, published by van Oers and colleagues, is one of the few studies that observed an OS benefit. There were 465 patients with relapsed follicular lymphoma randomly assigned to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or rituximab plus CHOP (R-CHOP). After this treatment, patients were again randomized to either observation or maintenance rituximab given every 3 months for 2 years. Results from this second randomization demonstrated that rituximab maintenance improved OS. At 3 years, the OS was 85% for the rituximab maintenance arm and 77% for the observation arm. However, the caveat is that the data were pooled for the CHOP and R-CHOP patients, so some of these patients did not receive rituximab up front. This is not how we currently treat patients, and whether the OS benefit would apply to R-CHOP-treated patients is debatable. Furthermore, it is unknown how many of these patients later received rituximab, which complicates the results. Therefore, this is a trial that shows an OS advantage, but there are caveats.

The other commonly cited data set that supports an OS benefit is a meta-analysis performed by Vidal and

colleagues. Their most recent analysis, published in 2011, examined 9 trials comparing maintenance rituximab with either observation or retreatment. The analysis found an OS benefit, primarily in the relapsed or refractory patients. However, some are not convinced by this data given the methodology used and because the OS benefit does not necessarily apply to the first-line patients.

H&O Could you describe some studies in which rituximab maintenance did not improve OS?

PB Yes, there are 4 important studies to mention. The first is a randomized trial conducted by the Swiss Group for Clinical Cancer Research, published by Martinelli and colleagues. In this trial, all of the patients with follicular lymphoma received single-agent rituximab, and the responders were randomly assigned to either observation or 4 additional doses of rituximab given at 2-month intervals (a much lower dosage than the typical 2-year maintenance regimen). The patients were rituximab-naïve, with 64 untreated patients and 138 patients previously treated with chemotherapy. The study had a median follow-up of 9.5 years, and the median event-free survival was 13 months for the observation arm and 24 months for the maintenance arm. There was a trend toward a survival benefit in the maintenance arm, but the study did not achieve the prespecified endpoint. Importantly, in previously untreated patients, 45% of the maintenance rituximab group had not experienced disease progression at 8 years, compared with 22% of the observation group. This is very encouraging, because it suggests that in some patients we can use minimal therapy and still get dramatic results.

The second study, published by Salles and colleagues, recruited patients with more advanced disease. This study included 1018 patients with a high tumor burden who responded to first-line chemioimmunotherapy (mostly R-CHOP, but also rituximab, cyclophosphamide, vincristine, and prednisone [R-CVP], and fludarabine-based therapy). Patients were then randomly assigned to 2 years of maintenance rituximab or observation. As expected, maintenance rituximab prolonged the time to next therapy and PFS (6-year PFS was 42% for the observation arm and 59% for the maintenance arm). This study had a long follow-up and found an increased PFS, but there were no differences in the rate of histologic transformation, response to subsequent therapy, or OS.

The final 2 studies have received a lot of press lately, and are changing the way we think about maintenance rituximab. These studies tested maintenance rituximab in largely asymptomatic patients, who typically are observed and not treated. In the first study, published by Ardeschna and colleagues, asymptomatic follicular lymphoma patients with low tumor burden were randomly assigned to observation,

4 doses of rituximab (ie, standard induction), or 4 doses of rituximab followed by maintenance rituximab for 2 years. The arm with only 4 doses of rituximab was closed owing to slow accrual, so the analysis compared observation with maintenance rituximab. Maintenance rituximab delayed the time to chemotherapy, but there was no change in histologic transformation or 3-year OS (94% in the observation arm and 97% in the maintenance rituximab arm). Despite the time to chemotherapy and PFS benefit, I think the real question remains unanswered. Longer follow-up is needed to determine if early intervention alters the natural history of follicular lymphoma, and if this can affect OS.

I think this last trial, published by Kahl and colleagues, is probably the most thought provoking and potentially practice changing of all the randomized studies. RESORT (Rituximab Extended Schedule or Retreatment Trial) is very different from the other studies I mentioned previously because it compared maintenance vs rituximab retreatment. The study enrolled previously untreated patients with low-tumor burden asymptomatic indolent lymphoma. Patients who responded to a 4-week rituximab induction were randomly assigned to maintenance rituximab until treatment failure or 4 doses of rituximab retreatment at the time of disease progression until treatment failure. This is a very different design than that of the previous trials, but it may be more pertinent to clinical practice. There were 289 follicular lymphoma patients who responded and were subsequently randomized. With a median follow-up of 4.5 years, there was no difference in the median time to treatment failure between the rituximab retreatment and rituximab maintenance strategies. Similarly to the study by Ardeschna and colleagues, an excellent OS was achieved—approximately 94% at 5 years in both groups. I think the most important conclusion of this study is that rituximab maintenance and rituximab retreatment appear equally beneficial in the asymptomatic population with regard to time to treatment failure. Because retreatment uses 3 to 4 times less rituximab, this strategy may be the most advantageous in this population.

There were also criticisms of this trial—for example, using time to treatment failure as the endpoint. Despite this, I think many investigators would conclude that retreatment is preferable to maintenance rituximab for patients with a low tumor burden. The next big question is whether this retreatment strategy can be extended to patients with higher-risk disease.

H&O Are there any explanations for the discrepancy between OS and PFS?

PB The median survival of follicular lymphoma patients is somewhere between 15 and 20 years. This means a very long follow-up period is needed to observe differences in OS, which is hard to achieve in our clinical trials. Additionally,

when we randomly assign patients to an observation arm, they can later receive rituximab off-study if they progress, which may obviate any OS benefit. In order to negate these problems, RESORT used the endpoint of time to treatment failure, which has a shorter follow-up time and may be more meaningful than PFS. In the future, we may need to follow patients longer for OS or design more creative endpoints in order to determine the benefit of maintenance strategies.

H&O Why would rituximab be used if there is no OS benefit?

PB Other markers of disease progression are significantly decreased by maintenance rituximab, so there are benefits other than OS. In RESORT, the patients receiving maintenance therapy achieved a delayed time to chemotherapy, which might be meaningful for some patients. For example, some patients are not fit enough for cytotoxic therapy, so prolonging their remission as long as possible with rituximab may be beneficial. However, because we now have nonchemotherapeutic options such as lenalidomide (Revlimid, Celgene) and idelalisib (Zydelig, Gilead Sciences), that argument may not be valid. There are also some patients who want to be more aggressive or proactive with their therapy, and the quality-of-life benefit in these patients may be a valid reason for giving maintenance rituximab. Overall, whether to give rituximab maintenance depends on the individual patient.

H&O How severe are the side effects of rituximab?

PB The side effects are not overwhelming, and I think most people would agree that they are very manageable compared with chemotherapy. We certainly see infusion reactions, but they are rarely severe, especially in the maintenance setting. The most notable side effects are neutropenia and infection. The rate of infectious complications in the randomized studies was approximately 2% to 10% in the maintenance rituximab patients and 1% to 3% in the observation patients. These were typically lower-grade upper respiratory tract infections or urinary tract infections, and were not severe in the majority of patients. One very severe but rare side effect is progressive multifocal leukoencephalopathy caused by reactivation of the JC virus, which can be life ending. However, I think that for the majority of patients the side effects are generally mild.

H&O Is quality of life changed by rituximab maintenance?

PB Quality of life does not appear to be altered in most studies. The only outlier, the study by Ardeshtna and colleagues, found that patients in the maintenance arm were

better able to cope with the lymphoma diagnosis. The difference in results may relate to the control group of patients receiving no therapy, which is likely associated with some degree of anxiety. Trials in which both arms get treatment can be less anxiety provoking and might have less impact on quality of life.

H&O Could you discuss the monetary costs and benefits of using maintenance rituximab?

PB The cost issue is obviously very real, and there have been a few analyses of cost effectiveness. One study, published by Hornberger and colleagues in 2012, found that the cost of maintenance rituximab is below currently accepted thresholds, making it worthwhile to use. Although there is cost associated with using this regimen, the treatment of relapsed disease is also expensive. However, as the health care system starts moving toward an accountable-care model, the value of expensive therapies will be increasingly scrutinized. This is obviously a very real issue that I think will continue to change with time.

H&O Do the results you mentioned apply to all follicular lymphoma patients?

PB These results do not apply to all follicular lymphoma patients. The majority of patients enrolled in the trials I mentioned had grade 1 or 2 follicular lymphoma. Grade 3B follicular lymphoma patients were excluded, and grade 3A patients were only the minority. The studies were also limited to patients who achieved an objective response. Therefore, all of these results are limited to grade 1 or 2 follicular lymphoma patients who responded well to rituximab initially.

Another problem is that the most commonly used first-line induction regimen for follicular lymphoma is typically bendamustine (Treaanda, Teva) plus rituximab (BR), which is only now being studied with maintenance rituximab. Most of the trials I mentioned used cyclophosphamide-based chemotherapy, so whether the data also apply to BR-treated patients is still unknown.

H&O Do you think it is worthwhile to use rituximab maintenance?

PB I think it depends on the patient. I keep both sides of the argument in mind, and spend a lot of time with patients discussing the pros and cons. It may be the longest patient meeting we have, but it is very important. I personally would not recommend using maintenance rituximab in asymptomatic patients with a low tumor burden, primarily based on RESORT. However, I think rituximab is still an option in patients who require

therapy, especially those receiving first-line rituximab plus chemotherapy, because in some patients a PFS benefit or delaying the time to second therapy may be worthwhile.

I think the use of maintenance rituximab will decrease in the future. Nationwide, quite a lot of the follicular lymphoma patients currently receive maintenance rituximab. However, based on RESORT and the changing concerns about the cost of health care, I think expert opinion is starting to sway against maintenance rituximab.

Suggested Readings

Ardeshtna KM, Qian W, Smith P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. *Lancet Oncol.* 2014;15(4):424-435.

Hornberger J, Chien R, Friedmann M, et al. Cost-effectiveness of rituximab as maintenance therapy in patients with follicular non-Hodgkin lymphoma after responding to first-line rituximab plus chemotherapy. *Leuk Lymphoma.* 2012;53(12):2371-2377.

Kahl BS, Hong F, Williams ME, et al. Rituximab extended schedule or re-treatment

trial for low-tumor burden follicular lymphoma: Eastern Cooperative Oncology Group protocol E4402. *J Clin Oncol.* 2014;32(28):3096-3102.

Martinelli G, Schmitz SF, Utiger U, et al. Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98. *J Clin Oncol.* 2010;28(29):4480-4484.

Nabhan C, Ollberding NJ, Villines D, et al. A systematic review of comparative schedule-related toxicities with maintenance rituximab in follicular and mantle cell lymphomas. *Leuk Lymphoma.* 2014;55(6):1288-1294.

Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet.* 2011;377(9759):42-51.

Tan D, Horning SJ, Hoppe RT, et al. Improvements in observed and relative survival in follicular grade 1-2 lymphoma during 4 decades: the Stanford University experience. *Blood.* 2013;122(6):981-987.

van Oers MH, van Glabbeke M, Giurgea L, et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. *J Clin Oncol.* 2010;28(17):2853-2858.

Vidal L, Gafter-Gvili A, Salles G, et al. Rituximab maintenance for the treatment of patients with follicular lymphoma: an updated systematic review and meta-analysis of randomized trials. *J Natl Cancer Inst.* 2011;103(23):1799-1806.