ADVANCES IN LLM

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

Section Editor: Susan O'Brien, MD

Is Rituximab Maintenance Still Standard of Care in Indolent Non-Hodgkin Lymphoma?

John P. Leonard, MD
Richard T. Silver Distinguished Professor of Hematology and Medical Oncology
Associate Dean for Clinical Research, Weill Cornell Medical College
Vice Chairman for Clinical Research, Department of Medicine
Associate Director, Weill Cornell Cancer Center
Attending Physician, New York Presbyterian Hospital
New York, New York

H&O What is the outlook for patients with indolent non-Hodgkin lymphoma (NHL)?

JL Indolent NHL comprises a group of chronic lymphomas. Although they are generally associated with long survival times, indolent lymphomas are considered incurable by conventional treatments. Follicular lymphoma is the most common indolent lymphoma. Other types include marginal zone lymphoma and small lymphocytic lymphoma. Indolent lymphomas typically grow slowly and often will be disseminated before a diagnosis is made. However, I believe the overall outlook is improving and will continue to do so. Patients are living longer, and re-treatment often yields considerable success, as long as the disease histology remains indolent, without transformation.

H&O Can you please differentiate between the management strategies of immediate versus delayed rituximab as upfront therapy in follicular lymphoma?

JL The former approach refers to using rituximab (Rituxan, Genentech/Idec Pharmaceuticals) as an early, immediate therapy—generally in patients with no or minimal symptoms and low tumor burden. Delayed therapy involves continuing to watch and wait before treating asymptomatic patients with indolent NHL. Rituximab is a targeted monoclonal antibody therapy, making it less toxic in some ways than chemotherapy. A large randomized study in the United Kingdom compared immediate rituximab with watchful waiting. At 3 years, patients receiving 4 weekly courses of rituximab induction therapy followed by 2 years of rituximab maintenance therapy every 2 months showed significant improvement when compared with the control arm in the time to initiation of the next treatment and in the time to progression. However, what was being compared was really time to first treatment (in the observation group) versus time to second treatment (in the rituximab group). Also, no major difference in quality of life was observed, and the overall survival was the same in each arm. Of note, treatment with single-agent rituximab was not generally employed as the "next therapy," as most patients received cytotoxic-based therapy when their disease progressed.

H&O What was the RESORT trial, and what are its implications?

JL The Eastern Cooperative Oncology Group E4402 protocol, also called RESORT (Rituximab Extended Schedule or Re-treatment Trial) was a randomized trial that included 545 untreated patients with stage III or IV indolent NHL and low tumor burden. Most patients had follicular lymphoma. The trial sought to determine whether a maintenance rituximab strategy following induction rituximab could improve time to treatment failure compared with a rituximab re-treatment strategy (without maintenance). All patients received

an induction regimen of 4 weekly doses of rituximab 375 mg/m^2. Patients who responded were randomized to rituximab maintenance therapy consisting of a single dose of rituximab every 3 months or treatment at the time of disease progression (rituximab re-treatment). Data were presented at the 2011 annual meeting of the American Society of Hematology (ASH) regarding 274 low tumor burden follicular lymphoma patients who responded to the induction regimen. The primary endpoint was time to treatment failure (TTTF), defined as disease that progressed within 6 months of the last rituximab treatment, disease that did not respond to therapy, need for alternative therapy, or inability to complete the treatment protocol. Secondary endpoints included time to first chemotherapy, quality of life (QOL), and safety. After a median follow-up of 3.8 years, TTTF was not different (3.9 years in the rituximab maintenance arm and 3.6 years in the rituximab re-treatment arm). The mean number of rituximab doses per patient, including the 4 induction doses, was 15.8 in the rituximab maintenance group and 4.5 in the rituximab re-treatment group. There was no discernible difference in health-related quality of life or burden of stress between the 2 arms 12 months after randomization. The investigators concluded that re-treatment, rather than maintenance therapy, was the preferred treatment strategy in this particular setting.

H&O What is the role of rituximab maintenance therapy after induction chemotherapy?

JL Rituximab was recently approved for single-agent maintenance therapy in patients with previously untreated follicular, CD20-positive, B-cell NHL who achieve a complete or partial response to rituximab in combination with first-line chemotherapy. The approval was based on results of the phase III PRIMA (Primary Rituximab and Maintenance) study, which compared rituximab maintenance therapy versus observation alone. The trial, which included 1,217 patients with untreated follicular lymphoma and high tumor burden, showed no benefit in terms of overall survival, but did show a progression-free survival benefit in subgroups. During maintenance therapy with rituximab, patients experienced more frequent adverse events, especially grade 2 infections, but very few patients withdrew from the study for treatment-related toxicities. There was no difference in a quality-of-life assessment between the treatment and observation arms. An unanswered question is whether re-treatment with rituximab at progression, rather than maintenance, could provide similar duration of benefit, as observed in the RESORT study.

H&O What are the key issues moving forward?

JL Although we have clear evidence of progression-free survival benefits in indolent lymphoma and more recently in mantle cell lymphoma, the overall survival benefits, particularly after chemoimmunotherapy and rituximab maintenance, remain to be determined. In fact, the RESORT trial suggested that either strategy might achieve the same benefit for the patient.

H&O Are there any new agents showing success in patients with indolent lymphomas when used as maintenance therapy?

JL Obinutuzumab (GA101) and ofatumomab are newer generation anti-CD20 antibodies that are undergoing comparison to rituximab in a number of settings. It is unclear whether they are superior to rituximab, particularly since, in most trials, they have been used at higher doses and for more treatments than rituximab is typically given. Additionally, lenalidomide (Revlimid, Celgene) is under evaluation in follicular lymphoma, both as initial therapy and in relapsed disease. Studies of maintenance lenalidomide, both alone and in combination, have demonstrated interesting results, and randomized trials are under way.

H&O What does the future hold?

JL A new generation of agents directed against molecular pathways associated with the pathobiology of indolent NHL are in clinical development so that the pathways most relevant to a given disease state can be targeted. GS-1101 and PCI-32765 target phosphoinositol 3-kinase (PI3K) and Bruton's tyrosine kinase (BTK), respectively. I think we will be seeing new developments that tend to move away from chemotherapy-based approaches, which will be beneficial to patients and hopefully more effective long-term. We need to capitalize on the clinical and biologic features of these diseases in order to develop more personalized treatment strategies using predictive biomarkers. Lastly, clinical trials need to establish better surrogate endpoints for survival, in order for regimens to be more rapidly evaluated and so that improvements upon standards of care can be quickly determined.

Suggested Readings

Ardeshna KM, Smith P, Qian W, et al. An intergroup randomised trial of rituximab versus a watch and wait strategy in patients with stage II, III, IV, asymptomatic, non-bulky follicular lymphoma (Grades 1, 2 and 3a). A preliminary analysis. *Blood* (ASH Annual Meeting Abstracts). 2010;116(suppl 21): Abstract 6.

Leonard JP, Martin P. Novel agents for follicular lymphoma. *Hematology Am Soc Hematol Educ Program*. 2010;2010:259-264.

Kahl BS, Hong F, Williams ME, et al. Results of Eastern Cooperative Oncology Group protocol E4402 (RESORT): a randomized phase III study comparing two different rituximab dosing strategies for low tumor burden follicular lymphoma. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract LBA6.

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;377:42-51.

Sehn LH, Goy A, Offner FC, et al. Randomized phase II trial comparing GA101 (obinutuzumab) with rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma: preliminary analysis of the GAUSS study. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 269.

Staudt LM, Dunleavy K, Buggy JJ, et al. The Bruton's tyrosine kinase (Btk) inhibitor PCI-32765 modulates chronic active BCR signaling and induces tumor regression in relapsed/refractory ABC DLBCL. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 2716.

Papadopoulos KP, Abrisqueta P, Chambers G, et al. A phase I dose expansion cohort study of the safety, pharmacokinetics and pharmacodynamics of SAR245409 (S09), an orally administered PI3K/mTOR inhibitor, in patients with Lymphoma. *Blood* (ASH Annual Meeting Abstracts). 2011;118(suppl 21): Abstract 1608.