Retreatment With Rituximab Offers a Similar Survival Benefit as Maintenance Therapy in Patients With Low Tumor Burden Follicular Lymphoma

A recent study regarding the use of rituximab in patients with low tumor burden follicular lymphoma demonstrates that retreatment with the drug at the time of disease progression provides long-term disease control that is comparable to that of maintenance rituximab (J Clin Oncol. 2014;32:3096-3102).

The authors of the Rituximab Extended Schedule or Retreatment Trial (RESORT) note that previous studies have shown that a strategy of maintenance rituximab after induction in patients with follicular lymphoma prolongs response duration. However, it is not clear whether this translates into truly improved long-term disease control. Researchers set out to address this question.

Together with colleagues from the Eastern Cooperative Oncology Group, RESORT study lead author Brad Kahl, MD, director of lymphoma service at the University of Wisconsin in Madison and clinical research director for hematologic malignancies at University of Wisconsin Carbone Cancer Center, recruited 408 previously untreated patients with low tumor burden follicular lymphoma. Patients with other low grade lymphomas were eligible, but were not reported in the current article. Low tumor burden was defined as no mass measuring greater than 7 cm, fewer than 3 masses measuring more than 3 cm, no systemic or B symptoms, no splenomegaly measuring greater than 16 cm, no organ compromise, no leukemic phase greater than 5000/µL circulating lymphocytes, and no cytopenias.

All patients were treated with rituximab at a dose of 375 mg/m² once a week for 4 weeks. Restaging was performed at 13 weeks and patients with stable or progressive disease were taken off the study. Patients with responding disease (289 patients) were randomized to observation with rituximab retreatment at the time of disease progression until treatment failure (143 patients) or scheduled maintenance rituximab of 1 dose every 13 weeks until treatment failure (146 patients). Retreatment consisted of weekly rituximab for another 4 weeks, which was repeated at each occurrence of progressive disease until treatment failure. Treatment failure was defined as no response to retreatment, time to disease progression of less than 26 weeks, initiation of alternate therapy, or inability to complete planned treatment. Treatment failure for patients on the maintenance arm was defined as any disease progression occurring between scheduled rituximab doses.

**SIMILAR SURVIVAL RATES**

With a median follow-up of 4.5 years, the estimated median time to treatment failure was 3.9 years and 4.3 years, respectively, for patients in the retreatment and maintenance arms (P=.54). The cumulative incidence of treatment failure at 3 years was 61% for the retreatment arm and 64% for the maintenance arm (P=.33); this difference remained nonsignificant in an analysis excluding those patients who withdrew for nonmedical reasons. A secondary endpoint of the study was time to first cytotoxic therapy, and for this endpoint the maintenance arm was found to be superior, with 95% of patients free of cytotoxic therapy at 3 years versus 84% of patients on the retreatment arm (P=.03).
Not surprisingly, patients who received maintenance therapy sustained their first disease remission longer: 78% at 3 years versus 50% of patients in the retreatment arm. The median response durations for patients in the retreatment arm progressively declined: 34.4 months after induction (143 patients), 18.5 months after first retreatment (56 patients), 12 months after second retreatment (12 patients), and no responses to a third retreatment (4 patients). No difference in overall survival was noted, with a 94% survival rate found in both arms at 5 years.

"Bottom line, a rituximab retreatment strategy provides comparable disease control to a maintenance strategy in low-tumor burden follicular lymphoma," says Dr. Kahl.

“In addition, a retreatment strategy is more cost-effective, as it requires about one-quarter as much drug utilization. For those 2 reasons, we recommend a retreatment strategy over a maintenance strategy in this patient population.”

The study found that grade 3 and 4 toxicities were uncommon in both arms, although one patient in the maintenance arm developed progressive multifocal encephalopathy and died. Patients’ quality of life and anxiety scores were measured during the study and no differences were noted between the treatment arms.

“This trial also speaks to the excellent outcomes in patients with low tumor burden follicular lymphoma no matter what you do,” says Jonathan Friedberg, MD, chief of hematology/oncology and director of the James P. Wilmot Cancer Center at the University of Rochester Medical Center in Rochester, New York. “Follicular lymphoma is a heterogeneous disease, but low tumor bulk is the most common presentation and these patients tend to do well over long periods of time. Maintenance therapy is probably overtreatment.”

IMPLICATIONS AND ONGOING QUESTIONS

The results of the current study indicate that the retreatment approach in patients with low tumor burden follicular lymphoma uses less rituximab and provides comparable disease control. The secondary endpoint of time to first cytotoxic chemotherapy did favor the maintenance arm, but not the endpoints of overall survival or quality of life. A cost analysis revealed that the cost difference was approximately $69,000 per patient, with the maintenance arm using substantially more resources.

“I feel confident in recommending against a maintenance approach, unless you have a patient who has extreme psychological distress associated with recurrence,” says Dr. Kahl. “For those patients, a maintenance strategy may be a reasonable choice. The onus is now on the treating physician to explain to the patient why they do not need maintenance, which is not intuitive to patients.” Dr. Kahl also points out that it is not known whether these findings can be extrapolated to the patient population with a high tumor burden, but suggests this will need further study.

Likewise, the current study does not address whether there are differences between a watch-and-wait upfront approach versus immediate rituximab induction and maintenance of low tumor burden follicular lymphoma. A recent study by Ardesha and colleagues did not demonstrate a survival difference between the 2 approaches, with 3-year survival rates exceeding 90% (Lancet Oncol. 2014;15:424-435).

“One can make a case for not treating these patients upfront at all, as there is no evidence yet that it improves survival,” says Dr. Friedberg. “Longer follow-up of the trial by Ardesha et al is needed to definitely determine whether early rituximab will affect transformation rates or long-term survival. NCCN [National Comprehensive Cancer Network] guidelines still recommend observation for upfront management of patients with low tumor burden follicular lymphoma outside of a clinical trial.”

Dr Friedberg also pointed out that approximately “30% of patients did not respond to rituximab induction. Finding biomarkers to identify these patients would be very helpful,” he says.

doi: 10.3322/caac.21255