Predictive Biomarkers May Help Individualize Treatment for Patients With Follicular Lymphoma

Researchers have identified a subgroup of patients with follicular lymphoma who derive greater benefit from bortezomib with rituximab versus rituximab alone (Clin Cancer Res. 2013;19:2551-2561).

Patients with follicular lymphoma, which is a heterogeneous disease, vary with regard to their disease course and responsiveness to treatment. As with other malignancies, there is an effort to individualize therapy by finding disease characteristics that predict responsiveness to a particular treatment. Predictive biomarkers would be especially helpful in patients with follicular lymphoma because there are multiple treatment options. Researchers set out to determine whether they could find such a tool to help individualize the treatment of patients with follicular lymphoma.

Bertrand Coiffier, MD, PhD, professor of hematology and head of hematology in the department of hematology at the Hospices Civils de Lyon and Claude Bernard University, both in Lyon, France, and his colleagues reported on a subset analysis of the previously reported phase 3 LYM-3001 study. The LYM-3001 study randomized nearly 700 patients with relapsed or refractory follicular lymphoma to receive bortezomib plus rituximab or rituximab monotherapy (Lancet Oncol. 2011;12:773-784). It demonstrated statistically significant improvements in the response rate (63% vs 49%) and progression-free survival (PFS) (12.8 months vs 11 months) for patients treated with bortezomib and rituximab versus those treated with rituximab alone, but no overall survival advantage was noted.

This subset analysis reports on an exploratory endpoint biomarker analysis that was preplanned in the study protocol. Potential biomarkers were prespecified and included proteins as well as genes that were chosen because of their attenuation by bortezomib, association with poor prognosis, or relation to rituximab activity.

Biomarker Pair Correlates to Response
Researchers first evaluated associations with single markers and found several markers that correlated significantly with PFS benefits, but the advantage was mostly fewer than 5 months or the frequencies were low. Next, analysis was performed pairing biomarkers and 1140 comparisons were made. In all, 14 biomarker pairs demonstrated a greater than 6-month increase in PFS for patients treated with bortezomib and rituximab versus those receiving rituximab alone.

One pair of biomarkers, the gene PSMB1 P11A C/G heterozygote and 50 or fewer CD68-positive cells, remained significantly associated with increased PFS with combination therapy after a statistical correction called the “false discovery rate” was applied. The cell number of CD68 was determined by taking the average of 3 separate high-power fields. This biomarker pair was subsequently tested under different genetic models. Researchers found that with low CD68, the PSMB1 P11A gene with the G allele (C/G3G/G) was significantly associated with PFS.

A total of 376 patients (186 of whom were treated with bortezomib and rituximab and 190 of whom were treated with rituximab alone) were evaluated for both the PSMB1 P11A gene and CD68 positivity. A total of 164 patients (44%) were biomarker positive, namely, they had the biomarker pair that was identified as being associated with better outcomes with the addition of bortezomib (PSMB1 P11A with the G allele and low CD68 expression). Of these, 78 patients were treated with bortezomib and rituximab and 86 were treated with rituximab alone. In biomarker-positive patients, PFS was found to be significantly longer in patients treated with bortezomib and rituximab versus those treated with rituximab alone (14.2 months vs 9.1 months; P < .0001).

The response rate was also significantly higher in the combination group. Overall survival appeared to be longer, with a hazard ratio of 0.49, but after statistical correction, it was not found to be statistically significant. No difference with regard to the safety of the regimens was noted between groups. In biomarker-negative patients, no difference in outcomes was noted between the treatment groups.
Results in Context

Dr. Coiffier says he considers the study results robust enough to recommend the biomarker pair as a basis for treatment choice, but it is not clear that the regimen of bortezomib and rituximab should be the treatment of choice among patients with follicular lymphoma.

“The question of whether this combination would be used in the treatment of follicular lymphoma will depend on the efficacy/toxicity of other possible treatments,” says Dr. Coiffier. “There are currently a lot of new, mostly targeted drugs available for this lymphoma and the future choices will depend on the results of not-yet-completed phase 3 studies.”

Bruce Cheson, MD, deputy chief of hematology-oncology and head of hematology at Georgetown Lombardi Comprehensive Cancer Center in Washington, DC, says it is critical to include correlative studies whenever possible in clinical trials, but knowing which studies to include is not always clear.

“Only through incorporating predictive biomarker evaluation in clinical trials will we eventually reach the goal of personalized treatments,” Dr. Cheson says. While he finds the current study intriguing, he believes its applicability is limited because the LYM-3001 trial did not meet the prespecified improvement in PFS that was written in the protocol, even though the addition of bortezomib significantly increased the PFS.

“We have more exciting novel agents in clinical trials for relapsed follicular lymphoma such as ibrutinib, idelalisib, IPI-145, and ABT-199,” Dr. Cheson adds. “For studies of these agents, correlative biomarker analysis will be critical for further development.”

The authors conclude that this prespecified subset analysis suggests that a predictive biomarker for increased PFS in response to the combination of bortezomib and rituximab exists in patients with follicular lymphoma. The study was one of the largest to date performed in patients with relapsed and refractory follicular lymphoma, adding to the strength of the findings. In addition, the biomarker analysis was planned, not a retrospective review of data. Furthermore, a high percentage of the population (43.6%) was biomarker-positive and combination therapy was found to significantly improve outcomes, thus indicating clinical usefulness.

However, the authors point out that it was an exploratory analysis, despite being prespecified in the protocol, making independent validation studies a requirement. Importantly, testing for the markers would be feasible; CD68 can be detected by immunohistochemistry and the authors state that the genotyping assay used to identify PSMB1 P11A was straightforward and that developing a validated assay for commercial use could be done.

The current study is a step in the direction of individualized therapy to improve outcomes in patients with lymphoma, but future work with other therapies is crucial. “There clearly will be other biomarkers in follicular lymphoma that will emerge as predictive for therapy response, such as current work looking at activity of the pathways related to the B-cell receptor,” Dr. Cheson says.

Dr. Coiffier agrees and adds that while multiple prognostic markers are well characterized, predictive markers for newer targeted agents are lacking and analysis of responding patients in phase 3 studies must be performed.

doi: 10.3322/caac.21197