

NEW DRUG REVIEW

Perspectives on Recent FDA Drug Approvals in Hematology and Oncology

Two New Indications for Rituximab

Brad S. Kahl, MD
Assistant Professor, Director Lymphoma Service
University of Wisconsin School of Medicine
and Public Health
Leader, Hematology Disease-Oriented
Working Group
Paul P. Carbone Comprehensive Cancer Center
Madison, Wisc.

H&O The US Food and Drug Administration recently approved two new indications for rituximab. Could you describe these?

BK The first indication is in combination with CVP (cyclophosphamide, vincristine, prednisone) chemotherapy in the first-line treatment of follicular non-Hodgkin lymphoma (FL). In this indication, rituximab (Rituxan, Genentech) is given concurrently with the chemotherapy. The second indication is for sequential use as part of first-line treatment of indolent low-grade lymphoma. In this indication, rituximab is given upon the completion of CVP chemotherapy, as 4 weekly doses every 6 months for a total of 2 years.

H&O Beginning with the first new indication, on what data is this approval based?

BK This approval is based on the results of an international randomized clinical trial in untreated FL.¹ In this study, approximately 321 patients with previously untreated advanced-stage disease were randomized to receive CVP with or without rituximab. Rituximab was administered to patients on the same day as the chemotherapy regimen for all cycles.

According to the study findings, published by Marcus and associates in *Blood*, adding rituximab to CVP resulted in improvements in virtually every endpoint measured. The overall response rate was 81% versus 57% for the rituximab-containing (R-CVP) and CVP-alone arms, respectively, with a complete response rate of 41%

versus 10%, respectively. Both of these measures were statistically significantly different for the two arms. The R-CVP arm was also associated with a significantly longer time to progression at a median follow-up of 30 months (32 vs 15 mo; $P < .001$). The median time to treatment failure—27 months versus 7 months, respectively—was also statistically significantly different between the two arms ($P < .001$). The 3-year overall survival rate was 89% versus 81%, respectively; this endpoint was borderline statistically significant ($P = .06$).

H&O Was toxicity exacerbated by the addition of rituximab?

BK No, the addition of rituximab did not increase the toxicity among patients receiving R-CVP.

H&O What is the significance of this new indication for patients with FL?

BK FL is a disease for which there are many good treatment options. The significance of this new indication is that adding rituximab to CVP improves response and progression-free survival without increasing toxicity. Previous studies with other combinations have shown improved response rates or prolongation of progression-free survival, but these improvements required the addition of more chemotherapy agents, leading to more toxicity. This new indication for rituximab has the benefit of improving outcomes without increased toxicity.

(Continued on page 934)

(Continued from page 901)

H&O Would R-CVP be a logical choice for the initial treatment of patients with FL?

BK Yes, absolutely.

H&O What data led to the second new indication?

BK The second new indication of rituximab—for the first-line treatment of patients with indolent low-grade lymphoma—was based upon the results of the Eastern Cooperative Oncology Group phase III trial E1496.²

In this randomized study, approximately 400 patients underwent CVP chemotherapy. Those with stable disease or who had achieved a complete or partial response (N=322) were then randomized to either maintenance rituximab or observation. Maintenance rituximab was administered in 4 weekly doses every 6 months for 2 years, for a total of 16 doses. The two groups were well balanced for clinical characteristics.

The findings, which have been presented at national meetings but are not yet published, showed a major advantage for maintenance rituximab: median progression-free survival was 4.2 years versus 1.5 years for the observation group.

H&O Indolent lymphoma comprises many lymphoma subtypes. Was this benefit seen in all subgroups?

BK Yes, the prolonged progression-free survival was observed in patients with follicular or other histology. The greatest benefit was seen among patients with follicular histology, those with a high tumor burden at study entry, and those who achieved a state of minimal residual disease after CVP chemotherapy.

H&O Why was CVP the chemotherapy regimen selected for these studies?

BK CVP is one of the more commonly used chemotherapy regimens in these disease settings. Other combinations could have been used; CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) and fludarabine-based combinations are also commonly used to treat patients with these types of lymphoma. Other studies have shown a benefit for the combination of rituximab plus either CHOP or fludarabine-based chemotherapy.

H&O Are there any important practical considerations for physicians incorporating these new indications into clinical practice?

BK Most physicians routinely incorporate rituximab into the treatment regimen for patients with FL or low-grade lymphoma and are thus comfortable with this approach. However, the question that remains to be answered is whether maintenance rituximab will add further benefit after initial treatment with rituximab plus chemotherapy. In the study described above, maintenance rituximab showed a benefit when given after CVP, but the initial chemotherapy did not include rituximab. Now, many clinicians are wondering whether patients who receive R-CVP or R-CHOP should then be given maintenance rituximab. Studies investigating this question are ongoing in Europe.

References

1. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood*. 2005;105:1417-1423.
2. Hochster HS, Weller E, Gascoyne RD, et al. Maintenance rituximab after CVP results in superior clinical outcome in advanced follicular lymphoma (FL): results of the E1496 phase III trial from the Eastern Cooperative Oncology Group and the Cancer and Leukemia Group B. *Blood* (ASH Annual Meeting Abstracts). 2005;106:349.