On RELEVANCE

Many effective treatment options exist for follicular lymphoma. Patients with low tumor burden can be managed initially with deferral of therapy (watch and wait). Patients with symptoms or high tumor burden typically are managed with rituximab plus chemotherapy (R-chemo). The chemotherapy choice varies from place to place. Bendamustine is quite popular in the United States, Germany, Italy, and Canada. CHOP is the regimen of choice in France. In the United Kingdom, they still use good old CVP chemotherapy. All are acceptable choices, with pros and cons. There may be a "chemo-free" option available in the near future that will be worth considering.

In case you did not have the opportunity to review the recent paper by Morschhauser, Fowler, and coauthors in the September 6 issue of the *New England Journal of Medicine*, I will summarize it here. The RELEVANCE trial compared the R^2 regimen (the novel combination of rituximab and lenalidomide) against R-chemo for frontline follicular lymphoma. Eligible patients had previously untreated, high–tumor burden follicular lymphoma. Lenalidomide was given at a dose of 20 mg/day for the first 21 of 28 days for 6 months, and then at 10 mg/day for 12 months. Rituximab was given throughout the 18 months of lenalidomide treatment, plus for an additional 12 months (total duration of treatment, 30 months). For the R-chemo control arm, individual treating physicians could choose CHOP, CVP, or bendamustine as their chemotherapy backbone, which was administered for 6 cycles, followed by 2 years of maintenance rituximab. The trial was designed to show superiority of the R^2 regimen over R-chemo, and the co–primary endpoints were complete response rate at 120 weeks and progression-free survival.

More than 1000 patients were enrolled in this international study. The two groups were well-balanced for important baseline characteristics, such as age, performance status, and FLIPI score. R-CHOP was the most commonly utilized control regimen (72%). With a median follow-up of 38 months, there was no difference in the complete response rate at 120 weeks, with 48% for R^2 and 53% for R-chemo. There was also no difference in the 3-year PFS, with 77% for R^2 and 78% for R-chemo. There was no difference in the risk of histologic transformation or in the risk of secondary cancers between the arms. The toxicity profiles were distinct. Neutropenia and nausea were more common with R-chemo, whereas rash and diarrhea were more common with R^2.

Because the trial did not prove superiority of R^2, I suspect that this regimen will not receive a frontline indication in follicular lymphoma. Had it been designed as a noninferiority trial, it might have met its primary endpoint. As they say, hindsight is 20/20. However, there is an ongoing study in relapsed follicular lymphoma, the AUGMENT trial, that is comparing R^2 against single-agent rituximab. My best guess is that R^2 will show superiority in that trial, which could/should lead to an indication in that setting. My understanding is that the AUGMENT trial will be presented at the 2018 American Society of Hematology meeting.

Proponents of R^2 like to call it "chemo-free" treatment. Whether it deserves that label is debatable. Lenalidomide has some significant side effects, including myelosuppression, venous thrombosis, and an increased risk for secondary cancers. It may not be genotoxic like classic DNA-damaging agents, but it is not completely benign either. Having said that, I am encouraged by these results. Even though RELEVANCE was a "negative" trial, it does teach us that R^2 is highly effective in follicular lymphoma. If the AUGMENT trial is ultimately positive and R^2 receives FDA approval in relapsed follicular lymphoma, then this regimen will become a very attractive option for patients. Based upon the RELEVANCE data, it is even conceivable that the NCCN guidelines committee may list R^2 as a frontline option. That would be fine with me. As I like to tell my patients, "it is always good to have options."

Until next month …

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Disclosure: *Dr Kahl served on the RELEVANCE data monitoring committee and has received consulting fees from Celgene.*