Re: Rituximab Maintenance for the Treatment of Patients With Follicular Lymphoma: Systematic Review and Meta-analysis of Randomized trials

Vidal et al. (1) reported on the use of rituximab maintenance for the treatment of follicular lymphoma. In contrast to their conclusions, we believe that there is insufficient evidence to routinely recommend maintenance rituximab following successful induction therapy in previously treated patients.

In their meta-analysis, the authors pooled data from five clinical trials of previously treated follicular lymphoma. They concluded that rituximab maintenance therapy, for up to 2 years, either as 4-weekly infusions every 6 months or as a single infusion every 2–3 months, should be added to standard therapy for patients with relapsed or refractory follicular lymphoma after successful induction treatment.

As pointed out by the authors, this meta-analysis has several limitations, including the use of various induction regimens (chemotherapy alone, rituximab alone, and chemotherapy with or without rituximab) and multiple maintenance schedules. Although, in statistical sensitivity analyses, these differences did not alter the main results, the restricted sample size did not provide adequate statistical power to assess potential influences by different induction and postinduction treatments.

Although Vidal et al. stated that the effect of rituximab maintenance therapy compared with rituximab at disease progression remains an open question in follicular lymphoma, they did not address this clinically important issue in the context of their own study. In one of the trials included in the meta-analysis, a study of 114 patients by Hainsworth et al. (2), patients in the control group were given rituximab at disease progression.

Figure 1. Three potential approaches for the delivery of rituximab which could improve the outcome of follicular lymphoma: A) maintenance schedule (chronic intermittent exposure), B) conditional schedule (up-front and relapse exposure), and C) dose–dense schedule (up-front intensive exposure). At this time, we do not know which approach is more beneficial (with respect to survival, safety, and cost-efficiency). Maybe they have similar survival outcomes, but different safety and cost outcomes? Properly controlled clinical trials are needed to address these clinically important questions.
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In the other four trials (3–7), rituximab treatment at relapse in the control group was not part of the studies and no information was provided on its use. Only the study by Hainsworth et al. (2) was designed to compare the benefit of maintenance rituximab vs rituximab at progression, and no difference in survival was found.

Although there is no doubt that patients with follicular lymphoma benefit from rituximab (2–7), it remains unknown if rituximab maintenance is more effective, safer, and/or cost-efficient compared with rituximab at disease progression. The present findings from the meta-analysis may simply reflect higher rituximab exposure in the maintenance compared with the control groups. Indeed, the absence of information on rituximab use in the control groups and its regulated use in some countries (1) are critical limitations with regard to the interpretation of observed associations. Theoretically, one could envision at least three potential approaches for the delivery of rituximab to achieve better outcomes: 1) maintenance schedule (chronic intermittent exposure), 2) conditional schedule (up-front and relapse exposure), and 3) dose–dose schedule (up-front intensive exposure) (Figure 1), all of which could have similar survival but different safety and cost outcomes.

In our opinion, the findings of the meta-analysis do not justify the authors' conclusion that maintenance rituximab should be added to standard therapy for patients with relapsed or refractory follicular lymphoma after successful induction therapy. Properly controlled clinical trials are needed to address this (2) and until these results are available, we would not recommend changing current clinical standards.

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References


Notes

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