Rituximab for follicular lymphoma: maintaining an open mind

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New data from the Primary Rituximab And Maintenance study provide the strongest support for the use of rituximab maintenance in patients with follicular lymphoma. However, further considerations of cost, inconvenience, toxic effects, efficacy of retreatment and lack of survival benefit should focus future clinical research on more-effective induction strategies.

Few drugs have made as great an impact on how patients with lymphoma are treated as the chimeric anti-CD20 monoclonal antibody rituximab. Chemoimmunotherapy regimens incorporating rituximab were the first strategies in decades to prolong the survival of patients with diffuse large B-cell non-Hodgkin's lymphoma (DLBCL), follicular lymphoma and chronic lymphocytic leukaemia. Moreover, rituximab is often the platform on which newer therapies are developed. However, until all patients are cured, there remains room for improvement in our treatments.

Given the already high complete response and overall response rates with chemoimmunotherapy, one attractive strategy has been to increase the duration of response with post-induction treatment, such as maintenance rituximab. Unfortunately, maintenance rituximab has not demonstrated a benefit in patients with DLBCL or chronic lymphocytic leukaemia. Nevertheless, the use of maintenance rituximab for the treatment of follicular lymphoma is widespread. Results from the Lymphocare study suggest that 45% of patients in the USA are being treated with this strategy following chemoimmunotherapy induction.[1] Indeed, new data from the Primary Rituximab And

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Maintenance (PRIMA) study provide support for the use of maintenance rituximab,[2] and will be discussed below.

What other available data are there to support the maintenance rituximab approach? Martinelli et al.[3] randomly assigned 202 patients to four weekly rituximab infusions followed by observation or maintenance using one dose every two months for eight months. At a median follow-up of 9.5 years, 45% of previously untreated patients remained event-free in the prolonged therapy arm compared with 22% in the control arm, but with no significant survival advantage (P=0.0813).

Ardeshna and co-workers conducted a three-arm randomised trial in which patients with stages II–IV, asymptomatic, non-bulky follicular lymphoma were randomly assigned to either watch-and-wait, weekly rituximab for four doses alone, or four doses of weekly rituximab followed by two years of maintenance.[4] Time to next therapy and progression-free survival (PFS) favoured the maintenance group. The controversial conclusion was that this approach should become the standard approach. However, the follow-up was only 32 months, there was no survival advantage, and many patients might still prefer to wait until progression before initiation of therapy, when more-effective treatments might become available. Moreover, there were no data on responsiveness to second-line therapy (first systemic treatment for watch-and-wait and second systemic treatment for rituximab-treated patients). Hochster et al.[5] treated patients with cyclophosphamide, vincristine and prednisone (CVP) followed by rituximab maintenance with four weekly doses every six

months for two years. Maintenance prolonged PFS, but not overall survival. Other groups evaluated maintenance rituximab in the relapsed setting, with prolongation of response duration or PFS[6] but without a significant overall survival benefit.

However, until now, no study had addressed the most important question: does maintenance rituximab improve the outcome of patients initially treated with the standard of care – chemotherapy plus rituximab? An important publication by Salles et al.[2] of the PRIMA study addresses this issue. Indeed, the FDA approved rituximab for maintenance therapy of follicular lymphoma in January 2011, a decision based largely on results from this trial. Previously untreated patients with follicular lymphoma were treated with R-CHOP (rituximab, cyclophosphamide, adriamycin, vincristine, prednisone), R-CVP (rituximab and CVP) or R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantrone) at the choice of the treating physician. Patients who achieved either a complete remission or partial remission were randomly allocated to either no further therapy or to rituximab maintenance every two months for two years (or until disease progression occurred). Of the 1217 patients who entered the induction phase, 503 underwent maintenance and 513 underwent observation alone. At a median follow-up of 36 months, the PFS was 74.9% in the maintenance arm compared with 57.6% in the observation arm (HR 0.55, 95%CI 0.44–0.68). The benefit was observed regardless of designated pretreatment characteristics including treatment regimen, age, sex, Follicular Lymphoma International Prognostic Index (FLIPI) or response to induction. In addition, event-free survival was improved in the group receiving rituximab maintenance. More patients were in complete remission at the end of maintenance than in the observation group. At the time of publication, there was no difference in overall survival because of the low number of events.

As maintenance rituximab consistently prolongs PFS, why not deliver it to all patients? Recognising that I am in the minority by avoiding maintenance rituximab, I will share my rationalisations. First, this therapy is expensive and time consuming. Moreover, the optimal maintenance schedule and duration are not known. In addition, there were more adverse events in the maintenance arm of the PRIMA study (56% vs 37%), notably grade 2–4 infections, with one death from fulminant hepatitis B.[2]

What is also not clear is whether maintenance provides an advantage over retreatment upon relapse. Many patients who had previously responded to rituximab respond again

to the same therapy, often with a longer response duration. Hainsworth et al.[7] randomly assigned relapsed and refractory patients to maintenance or retreatment upon relapse. Maintenance prolonged PFS, with no survival advantage.

The results of the RESORT trial (E4402; NCT00075846, which was completed in October 2008), in which patients received one weekly dose of rituximab for four weeks followed by either maintenance every three months until progression or observation with retreatment upon relapse, will be of interest to address this issue.

Second, there are toxic effects associated with maintenance rituximab including neutropenia, grade 3 and 4 infections,[8,9] and a small risk of potentially fatal, progressive multifocal leukoencephalopathy. Follicular lymphoma is a disease characterised by repeated relapses. Therefore, another concern is whether prolonged rituximab may compromise responsiveness to subsequent therapy.

In the CORAL study, Gisselbrecht and colleagues compared R-ICE (rituximab, iphosphamide, carboplatin, etoposide) versus R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin), both with stem-cell transplantation in relapsed DLBCL.[10] One of the strongest predictors of inferior outcome was receiving rituximab in a previous regimen. Data from the PRIMA study on responsiveness to salvage therapies are not yet available.

One alternative might be to use another agent after induction therapy. Potential candidates include radioimmunotherapy, newer antibodies such as humanised anti-CD20s, galiximab (anti-CD80), and epratuzumab (anti-CD22), lenalidomide, small-molecule proapoptotic agents, and signaling pathway inhibitors, such as those directed against Bruton tyrosine kinase or PI3K.

Although the PRIMA study provides the strongest support yet for the use of maintenance rituximab in patients with follicular lymphoma, some of us will continue to wait until studies demonstrate an impact on survival and any further complications that may appear over time as a result of maintenance rituximab. Most importantly, the availability of newer, more-effective targeted therapies may provide a solution – if you have better induction, then maintenance becomes irrelevant.

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Practice point

Maintenance rituximab prolongs progression-free survival of patients with follicular lymphoma, but may not yet be standard therapy for all patients.

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