Recent trials have demonstrated improvements in progression-free and overall survival with the inclusion of the chimeric anti-CD20 monoclonal antibody rituximab (Rituxan) in chemotherapy regimens for treatment-naive and relapsed patients with advanced-stage follicular non-Hodgkin's lymphoma (NHL). As rituximab therapy has significant single-agent activity in follicular NHL, is generally well tolerated, and has no dose-limiting or significant hematologic toxicity, a number of approaches evaluating maintenance therapy with extended dosing of rituximab are being tested. Trials have demonstrated prolonged progression-free survival in patients treated with maintenance rituximab using a variety of schedules following treatment with single-agent rituximab, induction or salvage chemotherapy, or salvage therapy with rituximab and chemotherapy combinations. Small increases in neutropenia and infections have been reported with extended rituximab use. Ongoing trials are evaluating the optimal use of rituximab (maintenance vs retreatment) and the benefit of rituximab maintenance following treatment of therapy-naive patients treated with rituximab-containing chemoimmunotherapy induction regimens. This article discusses the risks and benefits of maintenance rituximab for follicular NHL.

Immunotherapy with the chimeric anti-CD20 monoclonal rituximab (Rituxan) has rapidly gained acceptance in both initial and salvage therapy for patients with follicular lymphoma (FL). Chemoimmunotherapy with regimens such as R-CHOP (rituximab, cyclophosphamide, doxorubicin HCl, vincristine [Oncovin], prednisone), R-CVP (rituximab, cyclophosphamide, vincristine, prednisone), or R-MCP (rituximab, mitoxantrone, chlorambucil [Leukeran], prednisone) have been associated with improved outcomes, including longer duration of remissions and improvements in overall survival (OS).[1-3]

Several factors have contributed to this remarkable success. These include significant single-agent activity with acceptable infusion-related toxicity and, most critically, a lack of significant overlapping toxicity when rituximab is administered simultaneously or following conventional chemotherapy. This favorable benefit-to-risk ratio has led to studies using extended rituximab dosing as maintenance therapy following a variety of induction treatments. Nearly all such studies have demonstrated a benefit to maintenance therapy. This review will address the principles of maintenance therapy and the current data concerning the risks and benefits of the use of maintenance therapy with rituximab for patients with FL.

Defining 'Maintenance' Therapy

One of the difficulties in addressing this issue is a lack of definition of what constitutes "maintenance" therapy. In practice, there are two situations included in this category. In one case, rituximab is given as maintenance following an induction treatment regimen containing rituximab. This would include treatment with single-agent rituximab or the use of a rituximab-containing immunochemotherapeutic regimen. In the other situation, prolonged rituximab therapy is given following initial treatment with regimens not containing rituximab. This can also be thought of as sequential therapy. In this latter situation it is perhaps not as surprising that treatment with rituximab following chemotherapy would be better than chemotherapy alone as rituximab produces high levels of single-agent activity (50%-70%) in patients with de novo or relapsed FL.

Principles of Maintenance Therapy

Several principles contribute to the effectiveness of maintenance therapy. Obviously, maintenance treatment is neither necessary nor effective in patients cured by the primary treatment. In fact, the more effective the primary treatment is, the more difficult it may be to prove the effectiveness of a maintenance strategy. Effective treatments lead to a reduced frequency of—or a delay in time until—relapse, and may require larger studies or longer duration of maintenance and follow-up to prove benefit. Conversely, the effects of maintenance therapy with an active agent may be easier to
demonstrate when a high frequency and rate of events are observed following the induction therapy. In follicular non-Hodgkin's lymphoma (NHL), which is not currently considered curable by initial therapy, an increased rate/frequency of relapse is observed in a number of situations. These include the treatment of patients at higher risk (ie, higher Follicular Lymphoma International Prognostic Index [FLIPI] scores at diagnosis), treatment of relapsed patients (shorter expected subsequent remission rate and duration), and the use of less effective treatment regimens (lower response rates, complete response [CR] rates, and duration of remission).

A second important concept is that the disease must initially be, and must remain, sensitive to the agents given for maintenance. Thus, treatment of a population already resistant to the maintenance therapy is not beneficial and only exposes patients to the continued risks of the therapy.

**Development of Resistance to Rituximab**

It is clear that resistance to rituximab may be present at the time of initial therapy or may develop following rituximab exposure. In our initial trials with rituximab for relapsed indolent NHL, 48% of patients had a documented response (partial response [PR] plus CR) to treatment with infusions of 375 mg/m² weekly for four doses, with a median time to progression for responding patients of approximately 1 year.[4,5] Thus, at least 50% of these relapsed patients had some level of resistance to initial therapy with this regimen.

Furthermore, in a follow-up study, patients with a documented PR or CR to rituximab were then retreated upon disease progression with a second course of rituximab. All of these patients had previously responded with at least a PR or CR lasting more than 6 months, but only 40% had a documented response (PR or CR) to retreatment.[6] Thus, 60% of these patients developed some level of resistance to retreatment following prior therapy with rituximab. However, it is also true that only a minority of patients actually developed progressive disease on therapy and many had some response (defined as less than a PR, but not progression) to retreatment. Thus, there may still be some benefit in these situations.

In most cases, the mechanism of resistance to rituximab is poorly understood. Occasionally, this appears to be due to loss of the CD20 antigen,[7,8] but more often, antigen expression appears to persist, implying that the resistance must be due to either the loss of direct effects (cell signaling, growth inhibition, apoptosis) or to acquired resistance to the immune effector functions of antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).[9] In the context of a discussion on maintenance therapy, the question is: When during the course of therapy did this acquired resistance develop? Unfortunately, little information is currently available to help answer this question.

Patients with progressive disease while receiving rituximab maintenance, by definition, will be rituximab-refractory/resistant. It is reasonable to assume (but not proven) that patients refractory to rituximab therapy are unlikely to derive substantial benefit from rituximab maintenance therapy. As discussed below, it is not known how treatment with maintenance rituximab will influence the emergence of rituximab-resistant clones, nor what the clinical implications of this would be on subsequent therapy.

**Maintenance Therapy After Single-Agent Rituximab**

Our initial experience with single-agent rituximab for relapsed FL using a single dose and the weekly dose × 4 schedules did not identify a maximally tolerated dose or dose-limiting toxicity.[10,11] Further dose escalation was initially limited by drug availability. A subsequent study utilized eight weekly infusions for patients with relapsed FL, producing a similar response rate and duration of response to the weekly × 4 doses.[12]

Recent studies have clearly demonstrated that giving additional rituximab on an extended schedule can prolong remission durations. A phase II study evaluated treatment with repeated courses of rituximab (375 mg/m² weekly × 4), given at 6-month intervals for up to 2 years, to patients with stable or responding disease at 3 months following an initial course of rituximab.[13] Patients in this study had not received any prior therapy and had FL or small lymphocytic lymphoma. The time to disease progression was more than 34 months for the patients with FL, which is longer than reported outcomes of a single course of rituximab in patients with low tumor bulk.[14] Continued improvement in response was observed throughout the maintenance treatments.

A randomized study by the Swiss Group for Clinical Cancer Research (SAKK) provided more conclusive evidence. This trial evaluated patients with FL who were treated with four doses of rituximab on the usual weekly schedule.[15,16] Patients with at least stable disease were then
randomized to observation vs an additional infusion of rituximab (375 mg/m²) at months 3, 5, 7, and 9. The extended schedule resulted in prolongation of time to progression, both for patients without prior chemotherapy and for relapsed patients. Interestingly, there was no greater improvement in the response rate (PR, CR, or conversion of PR to CR) in the maintenance group compared with the observation group, with both arms demonstrating improvement following the initial evaluation time at 12 weeks from the start of treatment.

In this randomized study, the benefit of maintenance was limited to patients with a documented response (PR or CR) to the initial rituximab treatment. An advantage of using maintenance rituximab following initial treatment with rituximab is that one can judge the response to the initial rituximab and restrict the administration of maintenance to those who are sensitive to rituximab and who will receive the most benefit. This may make such an approach even more cost-effective.

**Maintenance Rituximab vs Retreatment With Rituximab at Relapse**

It is unclear whether it is better to prevent relapse with maintenance therapy or to reserve rituximab for retreatment of patients at the time of progression. One small clinical study has compared these two approaches.[17] Patients with at least stable disease after a course of four infusions of rituximab were randomized to receive maintenance rituximab (four weekly infusions of 375 mg/m², every 6 months for up to 2 years), vs retreatment with four weekly infusions of rituximab at the time of relapse. Patients responding to the retreatment were then observed until subsequent relapse and then treated again with a course of rituximab. The endpoints of the study, among others, included rituximab utilization (number of doses with each schema), duration of rituximab benefit, and response state and duration.

Not surprisingly, patients treated with maintenance rituximab enjoyed longer durations of remissions, and a greater percentage of patients remained in remission. In contrast, the retreatment group, as expected, experienced more frequent relapses. However, at the end of the study there was no difference in the duration of rituximab benefit. At the time of reporting, there was an increased use of rituximab in the maintenance group, but this difference was continuing to diminish as patients in the retreatment group continued to receive therapy at subsequent progressions.

Although this study did not demonstrate any definitive results, many investigators believe that the maintenance approach offers advantages, as the patient enjoys more prolonged clinical remissions. Opponents argue that maintenance costs, including drug and administration fees, make it difficult to justify this approach unless there is more definitive proof of benefit such as an improvement in overall survival.

A large US national trial is currently evaluating rituximab maintenance in patients with indolent NHL and low tumor burden (using Groupe d’Etude des Lymphomes Folliculaires [GELF] criteria) who respond to an initial course of rituximab. The Eastern Cooperative Oncology Group (ECOG) 4402-R, extended schedule or retreatment trial (RESORT), is randomizing these patients to continue treatment with rituximab (375 mg/m²) every 3 months until tumor progression vs retreatment with a course of rituximab at the time of tumor progression. This study is designed to determine which strategy leads to the most benefit and delays the time to the development of resistance to rituximab.

**Maintenance Rituximab After Chemotherapy Induction**

One large US trial (ECOG E1496) evaluated treatment with rituximab (375 mg/m² weekly × 4) every 6 months for up to 2 years for patients with stable or responding disease after treatment with either CVP or CF (cyclophosphamide, fludarabine) induction.[18] The CF arm was closed early following excess deaths associated with the chemotherapy. In FL patients after administration of CVP, the use of extended rituximab delayed the time to progression and was associated with a borderline improvement in overall survival. At 4 years, progression-free survival (PFS) for maintenance vs observation was 56% vs 33% and overall survival was 88% vs 72%, respectively. Patients in all risk groups benefited from sequential rituximab, but the greatest benefit was observed in patients with high tumor burden at the start of chemotherapy and minimal disease following chemotherapy.

Interestingly, in data presented at the 2007 annual meeting of the American Society of Clinical Oncology (ASCO), extended rituximab did not improve the outcome of patients in the small randomized subset of patients treated with CF induction chemotherapy.[19] The reason for this is not clear but appears to be associated with the higher CR rate of patients responding to this regimen and the lower number of events observed even in the patients assigned to observation. These "deeper" CRs may have decreased the frequency of relapse events so that a limited course of
The administration of rituximab maintenance therapy after induction with rituximab plus chemotherapy is becoming the most relevant situation in this setting, as most patients are now initially treated with the combination. Multiple randomized studies have demonstrated that rituximab added to CVP, CHOP, or MCP is superior (longer PFS and OS) to treatment with chemotherapy alone.[1-3] Is there a role for additional maintenance rituximab in this setting? Two trials have been reported evaluating this approach in patients with relapsed FL.

In a study by the German Low-Grade Lymphoma Study Group, maintenance rituximab was evaluated following R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantrone) or FCM chemotherapy.[20,21] The FCM arm was closed early due to the superiority of R-FCM at interim analysis, and the majority of patients were then treated with R-FCM. Patients responding to the induction arm were subsequently randomized to observation vs maintenance rituximab (375 mg/m² x 4 at months 3 and 9).[21] For 81 FL patients treated with R-FCM, maintenance therapy with rituximab was associated with prolongation of time to progression compared with observation (not reached vs 26 months, P = .035). In this study there was no significant increase in infections or toxicity associated with maintenance treatment.

In a study by the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON), patients with relapsed FL (who had received no prior anthracycline therapy or prior rituximab therapy) were randomized to R-CHOP vs CHOP.[22] Responding patients were subsequently randomized to observation vs rituximab maintenance (375 mg/m² every 3 months for up to 2 years). This study demonstrated the superiority of R-CHOP over CHOP, and not surprisingly, the use of maintenance rituximab delayed the time to progression/relapse in patients treated with CHOP. However, maintenance rituximab also significantly delayed the time to progression in those treated with R-CHOP. Median PFS was 33.1 months for R-CHOP/observation and not reached for R-CHOP/rituximab maintenance (P = .004). For the entire group, maintenance therapy improved overall survival at 3 years (85% vs 77%, P = .011). Slightly greater neutropenia and an increase in grade III/IV infections (9% vs 2.4%, P = .009) were observed in the maintenance group, but there were no treatment-related deaths associated with maintenance.

The key remaining question arising from these studies is whether these findings will be confirmed when rituximab maintenance is used following initial rituximab/chemotherapy induction in treatment-naive patients? Given the above data, it would seem reasonable to conclude that the results should be similar. However, it may be more difficult to demonstrate this benefit in the front-line setting since, among other reasons, patients generally have a much longer duration of remission following their initial therapy. Thus, there will be fewer events (relapses) expected in the first few years following treatment. The frequency and rate of events also depends on the efficacy of the initial treatment.

Although they are difficult to directly compare, nonrandomized studies suggest that PFS may be longer following R-CHOP than after R-CVP.[2,3] As maintenance is usually given for a limited duration, it may not be sufficient to prevent late relapses following a more effective induction therapy. In addition, patients who relapse early following rituximab/chemotherapy are likely already resistant to rituximab and would likely not benefit from additional rituximab given as maintenance. This may make it more difficult to demonstrate the benefits of maintenance in the front-line setting after increasingly effective rituximab/chemotherapy combinations.

The European Primary Rituximab and Maintenance (PRIMA) trial has now completed enrollment and is evaluating this question. Patients with treatment-naive FL were given a rituximab-containing chemotherapy combination (CHOP, CVP, FCM, MCP) and then randomized to observation vs rituximab maintenance (375 mg/m² every 2 months for 2 years). The choice of chemotherapy was not randomized, and the majority of patients received the R-CHOP regimen. Results are eagerly awaited. It is interesting to speculate that if this trial had been conducted with less effective initial therapy (perhaps R-CVP or rituximab alone), a greater number and frequency of events would have been expected and the effects of maintenance easier to demonstrate. In the absence of contradicting data, however, many clinicians are using maintenance following rituximab/chemotherapy induction, especially for patients at higher risk of early relapse (eg, with high FLIPI scores, bulky tumor, etc).

Potential Risks of Maintenance Rituximab
To date, only minimal infusion-related toxicity has been associated with the continued use of rituximab. However, as expected, extended rituximab administration does cause prolonged depletion of B cells from the peripheral blood and presumably from tissue compartments as well. In the SAKK trial, this finding was associated with decreases in serum immunoglobulin (Ig) M but not IgG.[15,16] In the HOVON study, IgG levels did not increase in the maintenance group, whereas they did in the observation group following CHOP or R-CHOP [22]. As discussed previously, increased neutropenia and an increase in treatable grade III/IV infections were associated with maintenance in this trial. One nonrandomized historical study reported severe hypogammaglobulinemia associated with serious infections in patients treated with fludarabine/rituximab combinations.[23] Patients with recurrent serious infections should have IgG levels checked, as IgG replacement may decrease their subsequent risk. This problem may increase with the use of maintenance rituximab. In addition, evidence suggests that the effects of rituximab impede the development of primary and secondary humoral immune responses.[24-26] This may have implications for the effectiveness of new vaccinations. Lastly, rituximab has been associated with the reactivation/progression of some chronic infections such as hepatitis B and, more recently, progressive multifocal leukoencephalopathy (PML), which may be fatal (US Food and Drug Administration [FDA] black box warning).[27,28] It is critical that studies evaluating maintenance rituximab look for and capture these events and that physicians counsel patients regarding these rare but serious and possibly fatal complications.

A maintenance approach may also have a strong impact on psychological, social, economic, or other factors. Maintenance treatments require scheduled treatments in the infusion room at a time when the patient is in remission. This increases the overall cost of the drug and administration, requires time off work, and may add psychological stress. On the other hand, staying in remission and avoiding additional treatment also has a major psychological benefit for most patients with FL. In a few situations where this has been studied, the economic impact of delaying tumor relapse appears to outweigh the economic cost of maintenance.[29]

Other potential risks, including the consequences of developing resistance to rituximab and the possible impact of this occurrence on subsequent treatments remain largely unknown. Comprehensive evaluation of these risks/benefits require well designed clinical trials with extended follow-up of patient outcome for both relapse and nonrelapse events. These risks suggest that, when possible, rituximab maintenance use should be guided by clinical trial results.

**Dose, Schedule, and Duration of Rituximab Maintenance**

As discussed above, a variety of administration schedules have been used for maintenance rituximab therapy. These have largely been empirically designed. One small trial involved pharmacokinetic analysis of antibody levels to guide the schedule of maintenance rituximab dosing.[30] A target of 25 μg/mL was empirically set, and single infusions of antibody were administered to keep the serum trough levels at or above this level. On average, following induction with four weekly doses of rituximab, additional rituximab was required every 2 to 3 months over the next year to achieve this result.

Based on this study and the results of the SAKK trial mentioned above, most ongoing trials are evaluating maintenance with a single infusion of rituximab every 2 to 3 months for 2 years or longer. In contrast, earlier studies evaluated four weekly infusions of rituximab given every 6 months for 1 to 2 years. While pharmacokinetic data are not available from these trials, data from the trial mentioned in the preceding paragraph demonstrate that the median time to antibody levels < 25 μg/mL following four infusions of rituximab was 5 months.[30]
As yet, no data suggest a benefit of using one schedule over another. However, based on the number of infusions required, most ongoing studies are adopting treatment with a single infusion every 2 to 3 months. Finally, the duration of optimal maintenance therapy is not known. Current trial data have been reported to a maximum of 2 years, and ongoing trials are evaluating longer maintenance durations. In the absence of safety data from longer-duration studies, a conservative approach seems prudent and maintenance treatment should be limited to a maximum of 2 years.

Conclusions

Extended rituximab therapy has been associated with prolonged PFS following chemotherapy or following rituximab induction for treatment-naive and relapsed patients with FL. In addition, maintenance rituximab improves PFS and OS of patients with relapsed FL who are treated with chemotherapy or rituximab/chemotherapy. Currently, the benefits of maintenance therapy appear to outweigh the risks. However, further data are needed to quantify the risks of hypogammaglobulinemia, neutropenia, and serious infections associated with extended maintenance.

Ongoing trials will help define the optimal dose and schedule, and hopefully determine whether a maintenance approach is superior to retreatment at the time of relapse. Currently available data suggest that maintenance rituximab should be considered in many situations for most patients with FL, especially those with higher-risk disease. Most importantly, it is critical that investigators continue enrolling patients into definitive clinical trials to further analyze the risks and benefits of this approach.

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