COUNTERPOINTS

Current Controversies in Hematology and Oncology

Is Maintenance Therapy Necessary in Low-Grade Lymphoma?

Maintenance therapy with rituximab has been shown to prolong progression-free survival and event-free survival in lymphoma, and it may even improve overall survival. Maintenance rituximab also involves toxicity and added expense, however, and long-term therapy might promote resistance to the drug. Here, Dr Paul M. Barr of the University of Rochester makes the case for using maintenance rituximab in patients with low-grade lymphoma, whereas Dr Chaitra Ujjani of MedStar Georgetown University Hospital argues against it.

Maintenance Rituximab Should Be Considered for Patients With Follicular Lymphoma

Paul M. Barr, MD, is an assistant professor of medicine at the James P. Wilmot Cancer Center at the University of Rochester in Rochester, New York.

The intent of maintenance therapy for patients with indolent non-Hodgkin lymphoma (NHL) is to prolong patient remission and survival, with the ultimate goal of achieving an effective "cure." The ideal maintenance strategy provides maximal benefit, carries minimal risk, and is convenient to administer. The agent that best fulfills these criteria for follicular lymphoma—the most common subtype of indolent NHL—is rituximab (Rituxan, Genentech/Biogen Idec). I believe that maintenance therapy with rituximab should be considered for patients with follicular lymphoma.

Initial attempts at maintenance therapy using interferon or cytotoxic agents did not provide an overall survival (OS) benefit, and were furthermore limited by side effects. The anti-CD20 antibody rituximab, however, has a favorable toxicity profile and a prolonged half-life. After rituximab was shown to improve outcomes in indolent NHL when added to induction therapy, it became an attractive agent to study in the maintenance setting.

The Research on Maintenance Rituximab

Nine prospective randomized clinical trials have evaluated maintenance rituximab (MR) for indolent NHL in various settings, including relapsed and previously untreated

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No Studies Have Shown Improved Overall Survival With Maintenance Therapy

Chaitra Ujjani, MD, is an assistant professor at the Lombardi Comprehensive Cancer Center at MedStar Georgetown University Hospital in Washington, DC.

The role of rituximab for maintenance therapy in the treatment of indolent NHL has been highly debated. Despite its proponents, available data from randomized trials raise doubt as to whether it is necessary.

Although maintenance therapy consistently has been associated with a longer PFS, an OS benefit has yet to be demonstrated. Additional issues to be considered include financial cost, toxicity, inconvenience to the patient, and allocation of hospital resources. A number of questions remain unanswered as well, including the optimal dosing schedule, the potential for anti-CD20 directed therapy resistance, and the impact on subsequent lines of therapy.

What the Evidence Says

The first trials that attempted to evaluate the utility of maintenance rituximab included different induction regimens—generally not including rituximab—followed by varying maintenance schedules. The Swiss Group for Clinical Cancer Research led the first study, SAKK 35/98, in which patients with follicular lymphoma received rituximab for 4 weeks, followed by either observation or 4 additional doses of rituximab every 2 months.[1] The median event-free survival was nearly twice as long with maintenance therapy as with

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disease. MR also has been studied following various induction regimens—including single-agent rituximab induction, chemotherapy, and chemoimmunotherapy—and using a variety of administration schedules. These studies consistently demonstrated that compared with observation, MR provides longer progression-free survival (PFS) and event-free survival (EFS), and may prolong OS. It is also well tolerated.

Single-agent rituximab provides effective disease control for many follicular lymphoma patients. MR following 4 weeks of induction rituximab can significantly prolong this effect, even with just 4 additional doses, as evidenced by the SAKK (Swiss Group for Clinical Cancer Research) 35/98 trial.[1] For this trial, Martinelli and colleagues enrolled 138 previously treated, rituximab-naive patients and 64 untreated patients, all of whom received standard rituximab induction. If patients were nonprogressive, they were randomly assigned to either observation or 4 additional doses of rituximab administered at 2-month intervals. After 8 years, 27% of patients receiving MR had not progressed or experienced another event, as compared with 5% in the observation arm. In the subset of previously untreated patients, 45% of MR patients had not experienced disease progression, compared with 22% of patients treated only with rituximab induction.

For patients with a high tumor burden, induction chemoimmunotherapy is often indicated. In the relapsed setting, MR has consistently provided a PFS benefit—as well as a trend toward an overall survival benefit following rituximab, cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisone (R-CHOP) in one study.[2] Given this signal, MR was evaluated following first-line chemoimmunotherapy in the PRIMA (Primary Rituximab and Maintenance) study.[3] More than 1000 patients responding to first-line chemoimmunotherapy were randomly assigned to 2 years of MR vs observation. Responses and PFS were statistically better in the maintenance arm regardless of the initial Follicular Lymphoma International Prognostic Index (FLIPI) score, the depth of response, or the induction chemoimmunotherapy used. As expected, MR also prolonged the time to next therapy. The PFS difference remained at 6 years, with 42% and 59% of patients in the observation and maintenance arms remaining progression free. No differences in the rate of histologic transformation, response to subsequent therapy, or OS were noted.

Studies of MR in asymptomatic patients with a low tumor burden are investigating a separate hypothesis. Evaluation of an OS benefit may be especially crucial in this setting, given the current practice of observation. Watchful waiting was originally established based on the lack of a survival benefit with early treatment in the era before rituximab, and prolonged disease stability in a proportion of patients with indolent NHL. Testing this practice, Ardeshna and colleagues randomly assigned patients with asymptomatic follicular lymphoma to watchful waiting, 4 weekly rituximab doses, or 4 weeks of rituximab followed by MR every 2 months for 2 years.[4] With early closure of the standard induction arm, the primary analysis compared observation with MR. As expected, MR delayed the time to chemotherapy. No OS difference has been observed to date. As such, longer follow-up is needed to determine if this early intervention alters the natural history of follicular lymphoma. Whether the beneficial impact of rituximab can be provided at disease progression instead of a continuous maintenance strategy in previously untreated patients with a low tumor burden is being investigated in the RESORT (Rituximab Extended Schedule or Retreatment) trial.[5] Enrolling asymptomatic patients with a low tumor burden, responders to the 4-week rituximab induction received either MR until disease progression, or rituximab retreatment at the time of disease progression. The preliminary findings suggest no difference in time to treatment failure. This suggests that this population may be served equally as well with the retreatment strategy, which uses 3 to 4 times less rituximab than the MR strategy. Whether these findings can be extended to patients with higher-risk disease is untested at this point.

> A meta-analysis found that patients treated with maintenance rituximab had a statistically improved overall survival.

The lack of an OS benefit in individual trials is not unexpected, given the long natural history of follicular lymphoma and the effectiveness of salvage therapy. To evaluate further the effect of MR on the OS of follicular lymphoma patients, a systematic review and meta-analysis of randomized controlled trials was performed that included 2586 patients from 9 studies comparing MR with observation or retreatment at relapse.[6] In addition to an improvement in PFS, patients treated with MR had

a statistically improved OS (pooled hazard ratio, 0.76; 95% CI, 0.62-0.92). This benefit was observed primarily in the relapsed or refractory patients, as an OS benefit was not observed in subgroup analysis of the first-line patients alone. These results may be potentially explained by the greater number of subsequent treatment options available for patients receiving MR after first-line therapy vs those with heavily pretreated disease.

In addition to the efficacy observed with MR, the rarity of severe toxicity further supports its use. Myelosuppression and infectious complications are most commonly observed. Infections occurred in 2% to 10% of MR patients, compared with 1% to 3% in observation cohorts; these typically represented grade 1 and 2 upper respiratory infections and urinary tract infections.[6] The incidence of infections increases with induction treatment that contains chemotherapy, and may be more frequent in heavily pretreated patients. As expected with such tolerability, discontinuation rates across the randomized studies were minimal.

Cost is another concern regarding the use of maintenance therapy, given the increasing expense of health care. A cost-effectiveness analysis of the PRIMA trial from a US payer perspective concluded that the increased cost of more than $38,000 for 2 years of MR was offset by gains in measures of health, including life-years gained and quality-adjusted life-years.[7] The authors thus argued that the cost of MR is below currently accepted thresholds, even using conservative assumptions in modeling long-term outcomes. Analyses in Sweden, France, and the United Kingdom have come to similar conclusions.[8-10] These studies remind us that for all of the cost associated with MR, the treatment of disease relapse is not exactly inexpensive.

Finally, quality of life does not appear to be diminished with the use of MR. Functional Assessment of Cancer Therapy-General (FACT-G) and European Organisation for Research and Treatment of Cancer (EORTC) global health status scores were no different in the MR and observation groups following chemoimmunotherapy induction in the PRIMA trial.[3] Ardeshna and colleagues demonstrated an improvement in scores evaluating the patient's ability to cope with the lymphoma diagnosis for those treated with MR as compared with observation.[4] No difference in quality of life outcomes was reported between the MR and retreatment arms of the RESORT trial.[11]

Conclusion

Taken together, these data support the use of MR—with some exceptions. Most of the patients enrolled to the randomized studies had follicular histology, with grade 3b follicular lymphoma being excluded and grade 3a disease accounting for only a minority of patients. Patients achieving a partial or complete response were most often included. As such, these findings are most applicable to grade 1 and 2 follicular lymphoma patients who achieve an objective response following induction therapy. Furthermore, given that bendamustine plus rituximab is now commonly used for induction, it is unclear whether the benefit of MR is similar. The PRIMA study would suggest a benefit in PFS following various chemoimmunotherapy regimens, based on the inclusion of R-CHOP, rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP); and rituximab, fludarabine, cyclophosphamide, and methotrexate (R-FCM).

The combination of consistent PFS improvement, OS benefit upon systematic review, minimal toxicity, convenient administration, and cost-effectiveness support the use of MR in follicular lymphoma when therapy is indicated, and this approach should be discussed with appropriate patients.

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observation; however, there was no significant difference in OS. In hopes of identifying a survival benefit, the SAKK 35/03 study compared the SAKK 35/98 regimen with 5 years of maintenance therapy.[2] Even with 4 additional years of rituximab, no improvement in OS emerged.

In the phase 3 intergroup study, ECOG 1496, patients with advanced-stage indolent lymphoma received 6 to 8 cycles of CVP; those who responded were randomly assigned to either 4 weekly doses of rituximab every 6 months for 16 doses, or observation.[3] Although PFS was better with maintenance therapy (P<.001), the OS was similar between the arms. ECOG 1496 was the study upon which the initial approval of rituximab for maintenance in indolent lymphoma after chemotherapy induction was based. Treatment decisions based on these data are somewhat irrelevant now, given that patients were not treated with chemoimmunotherapy, which is what would be considered the current standard for induction.

The PRIMA study was the first and only front-line phase 3 trial to evaluate the efficacy of maintenance rituximab following chemoimmunotherapy in high–tumor-burden follicular lymphoma (grade 1-3a).[4] More than 1000 patients received R-CVP, R-CHOP, or R-FCM at the discretion of their treating physicians. Those who achieved either a complete or partial response were stratified to either maintenance (rituximab every 8 weeks for 2 years) or observation. An updated analysis indicated that at 6 years, PFS was better with maintenance than with observation (59% vs 43%, P<.0001) but OS was nearly identical in the maintenance and observation groups (89% and 87%, P=.885). Furthermore, the incidence of death secondary to lymphoma was the same in both arms.

Both the EORTC and the German Low Grade Lymphoma Study Group (GLSG) investigated the use of maintenance therapy following rituximab-based regimens in relapsed/refractory follicular lymphoma. In EORTC 20981, patients received CHOP or R-CHOP followed by observation or maintenance (rituximab every 3 months for 2 years),[5] whereas patients in the GLSG study received FCM or R-FCM followed by observation or maintenance (4 weekly doses of rituximab at months 3 and 9).[6] While both studies showed an improvement in PFS with maintenance, there was no improvement in OS in either induction arm of the EORTC 20981 study. The GLSG did not report an improvement in OS in its original publication in 2006, and has not since then.

Even in low–tumor-burden follicular lymphoma, there does not appear to be a role for maintenance therapy compared with the watch-and-wait approach. In an intergroup study by Ardeshna and colleagues, previously untreated patients received either 4 weekly doses of rituximab (induction), rituximab induction followed by rituximab every 2 months for 2 years, or observation.[7] Based on preliminary results of the PRIMA study, the induction-alone arm was closed. Although both PFS and median time to next therapy were superior with maintenance therapy, there was no difference in OS or the risk of high-grade transformation.

Data from several of the previously mentioned studies, including PRIMA, were incorporated into a systematic review evaluating rituximab maintenance in follicular lymphoma.[8] In this meta-analysis, Vidal and colleagues reported that previously untreated patients did not achieve an improvement in OS after first induction, whereas those with relapsed/refractory disease did. Few conclusions regarding the efficacy of maintenance therapy ought to be gathered from this analysis, however. The induction regimens were inconsistent between the trials; many patients received either rituximab or chemotherapy instead of chemoimmunotherapy. The data were further confounded by the varying maintenance schedules, which differed considerably in interval and duration. Additionally, one study included patients who received autologous stem cell transplantation prior to maintenance therapy.

> Not only does maintenance therapy cause needless toxicity, it is expensive.

Toxicity and Cost

One salient point that can be gathered from the meta-analysis is that maintenance therapy is clearly associated with greater toxicity (RR, 1.60). In the intergroup study by Ardeshna and colleagues, 14 serious adverse events occurred with maintenance therapy.[7] In the PRIMA study, the rate of grade 2 to 4 infections was also significantly higher with maintenance therapy (P<.001).[9] Severe acute infectious complications, including hepatitis B reactivation and progressive multifocal leukoencephalopathy, can occur with rituximab, whereas long-term therapy can cause delayed toxicities such as hypogammaglobulinemia and neutropenia.

Not only does maintenance therapy cause needless toxicity, it is expensive. Because no consensus on the dosing schedule exists, patients can receive anywhere from 8 to 30 extra doses of rituximab. The resulting financial costs include not only the drug, but nursing, pharmacy, and facility fees. Early cost-effective analyses from the PRIMA study indicated that total costs in the United Kingdom with maintenance therapy were £14,129 higher than with observation.[10] Although the United States uses a significantly different payer model than the United Kingdom, one can assume that the costs of maintenance therapy would be significantly higher than no intervention.

Despite the PFS benefit of maintenance therapy, patients who are instead observed and treated upon progression have similar outcomes. This was evident in the ECOG-led RESORT study, in which patients with previously untreated low–tumor-burden follicular lymphoma received rituximab induction followed by either retreatment upon progression or indefinite rituximab.[11] There was no difference in time to rituximab failure, health-related quality of life, or anxiety between the arms. In addition, the study confirmed that patients could effectively be retreated with rituximab at the time of progression, obviating the financial costs and toxicities associated with prolonged exposure. Similar findings were noted in the PRIMA study as well.[4] The response to second-line therapy was the same, regardless of whether prior maintenance therapy had been used. Progression at an earlier point did not portend more aggressive disease, nor compromise the ability to induce a remission.

Interestingly, the improvement in PFS may not solely be attributable to maintenance therapy. In a pooled analysis of 3 prospective studies (PRIMA,[4] PET Folliculaire,[12] and FOLL 05 from the Fondazione Italiana Linfomi[13]), 246 patients were identified to have post-induction ^{18}F-fluorodeoxyglucose–positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scans. Patients with residual PET activity had a significantly inferior 4-year PFS and OS compared with those who became PET negative (P<.001).[14] In the subset analysis of patients from the PRIMA study, a PFS benefit of maintenance therapy was not seen.[15] With both observation and maintenance therapy, post-induction PET positivity was a strong predictor of an inferior PFS and OS, supporting the current belief that achieving a complete remission points to better long-term outcomes. It is unclear as to whether conversion from a partial to a complete response with maintenance therapy provides the same OS benefit as achieving a complete remission with induction. Thus, the focus of future trials should be improving the complete response rates of induction regimens with smarter, multi-targeted regimens. Current efforts to improve induction include 2 studies by the Alliance for Clinical Trials in Oncology: a Phase I Study of Rituximab, Lenalidomide, and Ibrutinib in Previously Untreated Follicular Lymphoma (NCT01829568) and a Phase I Trial of Lenalidomide, Rituximab, and Idelalisib in Recurrent Follicular Lymphoma (NCT01644799).

The PRIMA study prompted the US Food and Drug Administration to approve rituximab for maintenance therapy after rituximab-based chemoimmunotherapy in previously untreated follicular lymphoma. Before embracing this decision, however, the following issues should be considered: Is an improvement in PFS a sufficient trade-off for the increased risks and expense of maintenance therapy in the absence of a survival benefit? What are the long-term consequences of prolonged therapy? Is durability of response compromised by maintenance therapy? Although it looked at a different disease setting, the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study, which evaluated maintenance therapy after salvage chemoimmunotherapy in relapsed diffuse large B-cell lymphoma, suggested an inferior EFS for patients who received prior rituximab.[16] Because there has been no improvement in OS in any of these studies, do the data reflect a shortened duration of response to subsequent regimens following progression? Finally, as the United States health care system continues the vicious circle of inflated costs and poor reimbursements, is it not the physician's duty to act responsibly? If patients have the same life expectancy and maintain the same quality of life, is the more expensive option truly appropriate?

With the increased availability of novel biologic agents that are well-tolerated and more specific to the disease being treated, efforts should move away from maintenance treatment and toward creating superior regimens that improve OS and have a greater impact on the lives of patients.

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