Rituximab maintenance therapy: a step forward in follicular lymphoma

Marinus H.J. van Oers

From the Department of Hematology, Academic Medical Center, Amsterdam, The Netherlands

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Correspondence:
Marinus H.J. van Oers, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
E-mail: m.h.vanoers@amc.uva.nl

ABSTRACT

Whilst recent advances in the treatment of follicular lymphoma (FL) have improved the outlook for many patients, relapses still occur and the search continues for strategies to extend the duration of remission without significantly increasing toxicity. One such strategy is the use of rituximab maintenance therapy for patients responding to initial induction. There is now a large body of evidence demonstrating clear benefits of rituximab maintenance versus observation following induction with either rituximab plus chemotherapy (R chemo), chemotherapy alone, or rituximab monotherapy, in both first-line and relapsed/refractory settings. A very important finding is that rituximab maintenance can significantly improve overall survival in FL patients responding to induction with either R-chemo or chemotherapy alone. Also, compared with rituximab retreatment at disease progression, the maintenance approach produces much better complete remission rates and significantly longer continuous remissions and progression-free survival. Various maintenance schedules have been explored, all of which demonstrate clear benefits. However, the optimal dose, schedule, and duration of maintenance therapy still need to be established. Current data indicate that rituximab maintenance can be safely administered for up to 2 years, although assessment of long-term safety requires longer follow-up. From the patient's perspective, rituximab maintenance also prolongs the period in which patients are symptom-free and able to lead a relatively normal daily life. Also, rituximab maintenance may help patients feel they can control their disease, rather than *passively* waiting for relapse.

Key words: rituximab, maintenance therapy, follicular lymphoma.

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Indolent lymphomas, the majority of which are follicular lymphoma (FL), make up 30-35% of all non-Hodgkin's lymphoma (NHL) subtypes.[1] Historically, the course of indolent lymphoma has been characterized by initial responsiveness to single-agent or combination chemotherapy, with good response rates but frequent relapses. After the initial relapse, both the response rate and relapse-free survival decrease steadily, resulting in a median survival of 4-5 years after first relapse.[2] Transformation to an aggressive lymphoma subtype can occur at any stage of the disease and is associated with a very poor prognosis.[3] While recent advances in the treatment of indolent NHL have improved the outlook for many patients, relapses still occur and the search continues for strategies to extend the duration of remission without significantly increasing regimen toxicity. It is important to look further than just achieving remission in these patients and to use treatment strategies that prolong, as far as possible, the time patients remain disease-free.

One approach with the potential to prolong remission duration is the use of maintenance therapy in patients who have responded to initial induction therapy. Single-agent chemotherapy and combination chemotherapy maintenance schedules have been explored, to extend progression/relapse-free and overall survival (OS) in patients with indolent NHL. In a randomized study involving 111 patients in complete remission (CR) following induction therapy, maintenance chemotherapy with BCNU/BCVP administered every 6 weeks for up to 18 months significantly improved median progression-free survival (PFS) compared with no

further treatment and observation alone (p=0.02) but failed to provide any significant survival benefit.[4] In another study, patients with indolent NHL in remission after cyclophosphamide, vincristine, and prednisone (CVP) plus radiotherapy induction were randomized to intermittent chlorambucil maintenance for up to 2 years versus observation alone. Chlorambucil maintenance significantly prolonged relapse-free survival compared with observation alone (p=0.045), but failed to show any significant benefit in terms of OS.[5] In addition to the lack of demonstrable survival benefit, maintenance chemotherapy also raises concerns about long-term toxicities, and potentially increases the risk of secondary leukemias and myelodysplasia. Several clinical trials have explored the use of interferon-α2 (IFN) as maintenance therapy with conflicting results. In a clinical trial involving 98 patients with indolent NHL who achieved a CR after conventional chemotherapy induction, patients randomized to IFN maintenance administered three-times a week for up to 1 year achieved significantly longer remission duration (p<0.001) and median OS (p<0.001) compared with patients randomized to observation alone.[6] By contrast, in other randomized trials conducted in patients with indolent NHL, administration of IFN maintenance after chemotherapy induction did not produce significantly longer time to progression (TTP), PFS, or OS compared with observation alone.[7–10] Because of these conflicting results, a meta-analysis of 10 Phase III studies involving 1922 patients was carried out to evaluate the role of IFN in the treatment of newly diagnosed FL.[11] The authors concluded that a survival advantage was seen when IFN was combined with induction chemotherapy, but not when IFN was given as maintenance therapy after chemotherapy induction.[11] Furthermore, as Rohatiner and colleagues indicated, IFN toxicity was *not negligible*. This also questions its suitability for use in the maintenance.

The chimeric anti-CD20 monoclonal antibody rituximab was originally used as monotherapy for the induction of remissions in patients with relapsed indolent lymphoma.[12] It was subsequently combined with chemotherapy as induction therapy for patients with indolent lymphoma in both first-line and relapsed/refractory settings. Over the last few years, rituximab has been increasingly used as maintenance therapy in NHL and has so far produced very encouraging results. Rituximab is an attractive for maintenance therapy for a number of reasons. Firstly, rituximab is associated with only minimal acute toxicity and no major long-term or cumulative toxicity has yet been described. Secondly, although in the late 1990s there were a few reports of the loss of CD20 expression after rituximab therapy,[13,14] the CD20 target usually persists on residual or recurrent lymphoma cells allowing for successful retreatment. Finally, rituximab's long half-life allows for infrequent maintenance treatments while still maintaining long-term drug exposure which could, in principle, control residual malignant cells and delay disease recurrence. This infrequent administration in an outpatient setting is, of course, of particular importance to the patient. This article reviews the data that have emerged from key trials of rituximab maintenance therapy in patients with FL. Although some of these trials involved patients with different types of indolent lymphoma, the vast majority of patients had FL. Where possible, the data presented are restricted to patients with FL because, in our opinion, overall analyses of mixed cohorts of patients — with, for example, FL and chronic lymphocytic leukemia, or FL and mantle cell lymphoma (MCL) — are not very meaningful. Also, in most of these studies, the non-FL subgroups were too small to allow clear conclusions to be drawn.

Results with rituximab maintenance therapy in FL

Several key clinical trials have explored the use of rituximab maintenance therapy in patients with indolent NHL following induction with either single-agent rituximab, combination chemotherapy, or immunochemotherapy. These trials are discussed in more detail below.

Rituximab maintenance after induction with rituximab monotherapy

The Phase III Swiss Group for Clinical Cancer Research (SAKK) 35/98 trial was initiated in January 1998 and enrolled both newly diagnosed (n=64) and previously treated (n=138) patients with FL. Overall, 151 patients (51 of whom were previously untreated) achieved CR, partial remission (PR), or stable disease after rituximab monotherapy induction (four once-weekly doses) and were subsequently randomized to either no further treatment or rituximab maintenance therapy consisting of four single rituximab infusions administered at 2-month intervals.[15] At a median follow-up of 35 months, median event-free survival (EFS) among all patients receiving maintenance therapy was significantly longer than that achieved by patients receiving no further treatment (23 versus 12 months; p=0.024) (Figure 1). Also, subgroup analyses demonstrated that rituximab maintenance approximately doubled EFS in chemotherapy-naïve patients (median EFS 36 months with maintenance versus 19 months with no further treatment; p=0.009) and in patients responding (CR/PR) to induction therapy (median EFS 36 months with maintenance versus 16 months with no further treatment; p=0.004).[15] Rituximab maintenance was well tolerated, and among 137 patients who were evaluable for toxicity beyond 1 year, incidence was only 7% in both treatment arms. This demonstrates that rituximab maintenance doses did not cause additional toxicity after rituximab monotherapy

induction. Despite the small number of patients in some of the subgroups due to the heterogeneity of patients included in the trial, overall this study showed that rituximab maintenance after rituximab monotherapy induction significantly improves outcomes in FL in terms of both response duration and EFS, without causing additional toxicity.

Two phase II trials of rituximab maintenance therapy after rituximab monotherapy induction have been conducted by the US-based Minnie Pearl Cancer Research Network. Each of these studies explored the use of a maintenance schedule consisting of four once-weekly rituximab infusions repeated at 6-month intervals for up to 2 years.[16–18] The first of these studies was a small Phase II, single-arm study involving 62 patients with previously untreated indolent NHL (61% FL, 39% small lymphocytic lymphoma [SLL]), which was started in March 1998. The study evaluated the safety and efficacy of four once-weekly 375 mg/m^2 doses of rituximab induction followed by rituximab maintenance for patients with CR, PR, or stable disease at Week 6 after induction.[16,17] At Week 6, objective responses (ORs) or stable disease were noted in 28/60 (47%) and 27/60 (45%) evaluable patients, respectively. These patients were eligible to subsequently receive maintenance therapy. Of these patients 46 received at least one course of rituximab maintenance. Sixteen out of 27 patients (59%) who initially achieved stable disease at Week 6 achieved ORs with rituximab maintenance. Overall, 25 patients (42%) improved their initial response category as a result of maintenance therapy, producing final OR and CR rates of 73% and 37%, respectively.[16] At a median follow-up of 55 months, median actuarial PFS for the overall cohort was 37 months, with a 5 year actual PFS rate of 34%.17 Median PFS was significantly longer in patients with FL than in those with SLL (52 versus 31 months; p=0.04), and the actuarial 5-year OS rate (overall cohort) was 70%.[17] Rituximab induction was well tolerated and rituximab maintenance was not associated with any grade 3/4 toxicity.[16,17]

Maintenance versus retreatment

In a second Minnie Pearl Cancer Research Network-coordinated randomized Phase II trial started in June 1998, 90 out of 114 patients with relapsed or refractory indolent NHL (62 with FL, 28 with SLL) who had achieved CR, PR, or stable disease after four standard once-weekly doses of rituximab induction were randomized to receive either rituximab maintenance (four once-weekly doses repeated at 6-month intervals for up to 2 years) or rituximab retreatment (four once-weekly doses) at disease progression.18 In the maintenance arm, 6 additional ORs were achieved with maintenance therapy, increasing the OR rate from 39% (after induction) to a best response rate of

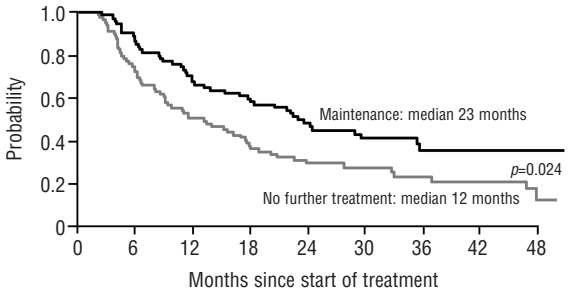

Figure 1. Event-free survival in patients receiving rituximab maintenance therapy or no further treatment following rituximab induction therapy for previously untreated or relapsed/refractory indolent NHL: SAKK 35/98 trial.[15]

52%, with an increase in CR rate from 9% (after induction) to 27%. By contrast, patients who were retreated at disease progression demonstrated a minimal change in the OR rate (33% after induction to 35% after retreatment) and only 2 patients in the retreatment arm (4%) achieved CR at any time during treatment. The median follow-up period for all patients in this trial was 41 months. Median PFS was significantly prolonged in the maintenance group compared with the retreatment group (31.3 versus 7.4 months; p=0.007) (Figure 2).

Similarly, in the subset of patients with FL, median PFS was longer in the maintenance arm than the retreatment arm (31 versus 13 months respectively). Also, more patients in the maintenance arm achieved continuous remission (20 patients in the maintenance arm versus 11 in the retreatment arm; p=0.05) and were in CR at study end (10 patients in the maintenance arm versus 1 in the retreatment arm; p=0.03). However, there was no significant difference in 3-year OS rates between the two arms (72% with maintenance versus 68% with retreatment).[18] Furthermore, there was no difference between both groups in *rituximab benefit*. This was defined as time from date of study entry to date of next (non-rituximab) lymphoma treatment required (31.3 versus 27.4 months in the maintenance and observation arms respectively). It is important to note that the cumulative rituximab dose administered was approximately 29% lower in the retreatment group. Both rituximab maintenance and rituximab retreatment were well tolerated -there were no treatment-related hospitalisations and no patient discontinuations resulting from treatment-related events.

Unfortunately, assessment of quality of life was not part of this rather small study in a heterogeneous group of patients. The important issue of maintenance treatment versus retreatment upon relapse is the subject of large ongoing randomized Phase III study (RESORT trial; see Table 1.

Rituximab maintenance after chemotherapy induction

A Phase III trial conducted by the Eastern Co-operative Oncology Group (ECOG 1496) was started in March 1998. In this study, 305 evaluable patients with newly diagnosed advanced indolent NHL (78% of whom had stage III/IV FL) achieving CR, PR, or stable disease following CVP induction chemotherapy were randomized 1:1 to either rituximab maintenance therapy (four once-weekly doses repeated at 6-month intervals for up to 2 years) or observation alone.[19,20] At a median follow-up of 3 years, overall PFS was significantly prolonged in patients who received rituximab maintenance compared with those in the observation arm (median 4.2 versus 1.5 years; p=0.00003).19 This cohort included a subset of 237 patients with FL (median age 58 years, 65% with stage IV disease, 64% with bone marrow involvement, 64% with high tumor burden, 37% with high-risk disease). Analyses conducted in this subgroup revealed a highly significant PFS benefit with maintenance therapy compared with observation alone (median PFS: 61 versus 15 months; p=3 x 10^{-7}; Hazard Ratio [HR] 0.4).[20] The improvement in PFS associated with rituximab maintenance versus observation was present in all Follicular Lymphoma International Prognostic Index (FLIPI) subgroups, but was particularly significant among patients with initial high tumor burden and patients with only minimal residual disease after CVP (Table 2). Importantly, OS was significantly prolonged in patients with FL who received rituximab maintenance compared with those randomized to observation alone (OS at 42 months from randomization and 48 months after completing CVP induction: 91% versus 75%; p=0.03; HR 0.5).[20] Furthermore, of the 33 deaths that occurred on-study in the subset of patients with FL, only 12 (36%) occurred in the maintenance arm, compared with 21 deaths (64%) in the observation-only arm.[20] PFS and OS data 3 years post-randomization in the maintenance and observation arms in patients with FL stratified by FLIPI score, tumor burden, and degree of residual disease are summarized in Table 2.[20] Overall, these data demonstrate that rituximab maintenance therapy significantly delays disease progression in FL compared with observation alone and that a substantial number of patients receiving rituximab maintenance remain disease-free 4 years after completing CVP induction. Furthermore, while longer-term follow-up is necessary to assess the full impact of rituximab maintenance therapy on OS in patients with FL, this study provides strong evidence that rituximab maintenance has a significant survival benefit in FL. Also, rituximab maintenance was well tolerated and did not lead to significantly higher rates of neutropenia, thrombocytopenia, or infection compared with observation alone.[19,20]

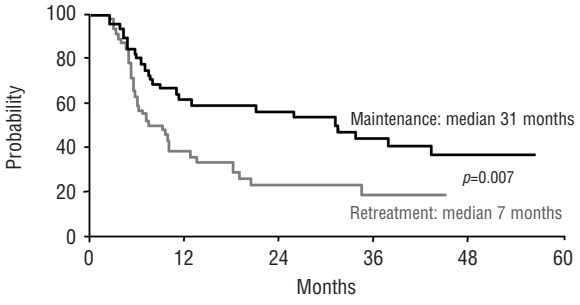

Figure 2. Progression-free survival after rituximab maintenance therapy or retreatment with rituximab at progression following rituximab induction therapy for relapsed/refractory indolent NHL: Minnie Pearl Cancer Research Network trial.[18]

Table 1. Major ongoing trials of rituximab maintenance therapy in FL.

Trial name or reference	*Previous treatment*	*Treatment*
		Rituximab maintenance after immunochemotherapy
PRIMA trial	UT FL	I: 8 x R-CVP vs 8 x R + 6 x CHOP vs 8 x R + 6 x MCP vs 8 x R + 6 x FCM M: R maintenance vs Obs
OSHO/GLSG	UT FL	I: 8 x R CHOP vs 8 x R MCP vs 6 x R FCM trial M: 1 x R every 2 months for 2 years vs interferon maintenance
Italian Multicenter trial	UT FL	Elderly patients (aged 60–75 years) I: 4 x R-FND, then patients with CR/PR/SD receive once-weekly R x 4 M: 1 x R every 8 weeks for 4 doses vs Obs
		Rituximab maintenance after rituximab monotherapy
RESORT trial	UT FL	I: Once-weekly R x 4 M:1 x R every 12 weeks until disease progression vs R retreatment upon progression
"Watch and Wait" trial	UT FL	"Watch and wait" vs once-weekly R x 4 vs once-weekly R x 4 + 1 x R every 2 months for 1 year
SAKK 35/03 trial	PT/UTFL	I: Once-weekly R x 4 M: 1 x R every 2 months for 4 doses vs 1 x R every 2 months for 5 years

CR: complete remission; FCM: fludarabine, cyclophosphamide, mitoxantrone; FL: follicular lymphoma; FND: fludarabine, mitoxantrone, dexamethasone; GLSG: German Low Grade Lymphoma Study Group; I: induction therapy; M: maintenance therapy; MCP: mitoxantrone, chlorambucil, prednisolone; Obs: Observation; OSHO: Ostdeutsche Studiengruppe Hämatologie/Onkologie; PRIMA: Primary Rituximab and Maintenance A; PR: partial remission; PT: previously treated; R: rituximab; R CHOP: rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisolone; RESORT: Rituximab Extended Schedule Or ReTreatment; R FCM: rituximab plus fludarabine, cyclophosphamide, mitoxantrone; R MCP: rituximab plus mitoxantrone, chlorambucil, prednisolone; SAKK: Swiss Group for Clinical Cancer Research; SD: stable disease; UT: previously untreated.

Rituximab maintenance after immunochemotherapy induction

In 1998, a Phase III intergroup trial co-ordinated by the European Organisation for Research and Treatment of Cancer (EORTC) Lymphoma Group was

Table 2. Progression-free survival (PFS) and overall survival (OS) in FL patients at 3 years from randomization to rituximab maintenance therapy or observation according to baseline disease characteristics: ECOG 1496 trial.[20]

Characteristic (n)	PFS Rituximab maintenance	PFS Observation	PFS p value	OS Rituximab maintenance	OS Observation	OS p value
FLIPI score						
0–2 (118)	59%	36%	0.002	94%	88%	0.08
3–5 (68)	58%	35%	0.004	91%	70%	0.16
Tumor burden						
Low (85)	65%	51%	0.025	93%	99%	0.38
High (152)	59%	28%	<0.0001	92%	74%	0.01
Residual disease						
Minimal (137)	73%	41%	<0.0001	95%	90%	0.11
Gross (100)	48%	30%	0.005	89%	75%	0.08

ECOG: Eastern Cooperative Oncology Group; FL: follicular lymphoma; FLIPI: Follicular Lymphoma International Prognostic Index.

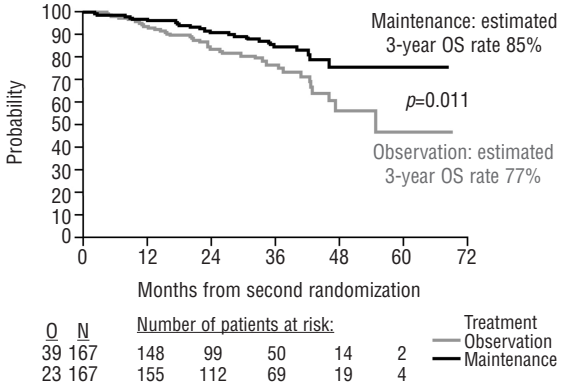

Figure 3. Overall survival (OS) after rituximab maintenance therapy or observation only in patients with relapsed/refractory follicular lymphoma responding to induction therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone with or without rituximab.[21]

started by a number of groups in Europe, Canada, and Australasia. The objectives of this study (EORTC 20891) were: (i) to evaluate the impact of adding 6 doses of rituximab to 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) induction chemotherapy on the rate and quality of response in patients with relapsed FL; and (ii) to evaluate the impact of subsequent rituximab maintenance therapy (a single 375 mg/m^2 infusion once every 3 months for up to 2 years) on PFS in patients achieving CR/PR after induction.[21]

R CHOP induction therapy produced a significantly higher CR rate compared with CHOP induction alone (29.5% versus 15.6%; p<0.0001), which translated into a significantly prolonged median PFS from first randomization (33.1 versus 20.2 months; p=0.0003). Furthermore, the addition of rituximab to CHOP did not increase the toxicity of induction therapy. Patients achieving CR or PR after 6 cycles of induction therapy subsequently underwent a second randomization to rituximab maintenance or no further treatment (observation alone). PFS from the second randomization (R-CHOP and CHOP patients combined) was significantly prolonged in the maintenance arm compared with the observation arm (median 51.5 versus 14.9 months; p<0.0001) and, importantly, the estimated OS rate 3 years after second randomization was significantly higher in patients receiving rituximab maintenance than in those who received no further treatment and were only observed (85.1% versus 77.1%; p=0.0111; Figure 3).[21] Compared with observation alone, rituximab maintenance therapy significantly improved PFS after both CHOP (median 42.2 versus 11.6 months; P<0.0001; Figure 4A) and R-CHOP (median 51.8 versus 23.0 months; p=0.0043; Figure 4B), and in patients entering the maintenance phase in both CR (median 51.6 versus 14.5 months; p=0.0009) and PR (median 45.4 versus 15.6 months; p<0.0001).

Rituximab maintenance treatment was associated with minimal toxicity - only 6 out of 167 patients (4%) had to discontinue treatment because of toxicity, 4/6 due to infections, and there was no treatment-related mortality.[21] Overall, these data suggest that rituximab maintenance therapy after immunochemotherapy can significantly improve survival in patients with relapsed or refractory FL.

A Phase III trial conducted by the German Low Grade Lymphoma Study Group (GLSG) enrolled patients with relapsed FL, MCL, or lymphoplasmocytoid lymphoma between November 1998 and June 2001. Patients were initially randomized to treatment with fludarabine, cyclophosphamide, and mitoxantrone (FCM), with or without rituximab,[22] and those responding to treatment underwent a second randomization to either rituximab maintenance (four once-weekly doses at 3 months and 9 months after induction) or observation alone.

Patients who received R FCM induction therapy achieved significantly higher CR and OR rates than those who received induction with FCM alone (CR: 33% versus 13%; p=0.005; OR: 79% versus 58%; p=0.01),[22] which translated into significantly longer OS in the R FCM arm versus the FCM arm, both for patients with FL (74% at 4 years versus median 3.8 years; p=0.033) and MCL (median 2.5 years versus 0.9 years; p=0.031).[23] The first randomization was stopped after 147 patients because of the significantly improved outcomes in patients treated with R FCM. All subsequently enrolled patients received R FCM induction. A total of 176 evaluable patients responding to induction (138 and 38 of whom had received R-FCM and FCM induction, respectively) underwent a second randomization to either rituximab maintenance (n=85) or observation alone (n=91).[24] Compared

with observation alone, rituximab maintenance therapy significantly improved duration of response in patients responding to induction with FCM ± R (n=176; $p<0.001$). After response to R-FCM induction, rituximab maintenance significantly prolonged response duration in the subgroups of patients with FL (n=81; $p=0.035$) and MCL (n=47; $p=0.049$), as well as in patients with FL, MCL, and lymphoplasmocytoid lymphoma combined (n=138; $p=0.001$). At present, no statistically significant improvement in OS has been demonstrated with maintenance therapy versus observation in either the overall group or the FL and MCL subgroups.[24] Once again, although involving a limited and heterogeneous patient group, this study suggests that all patients with FL and MCL can benefit from rituximab maintenance whether or not they have received rituximab as part of their induction regimen. These two studies (EORTC 20891 and the GLSG trial) clearly demonstrate the benefits of rituximab maintenance therapy after successful induction with immunochemotherapy in patients with relapsed indolent NHL. Based on these encouraging data, the Primary RItuximab and MAintenance (PRIMA) trial of rituximab maintenance versus observation alone after a variety of immunochemotherapy regimens in previously untreated indolent NHL is now underway to evaluate the benefits of this treatment pattern in a first-line setting.

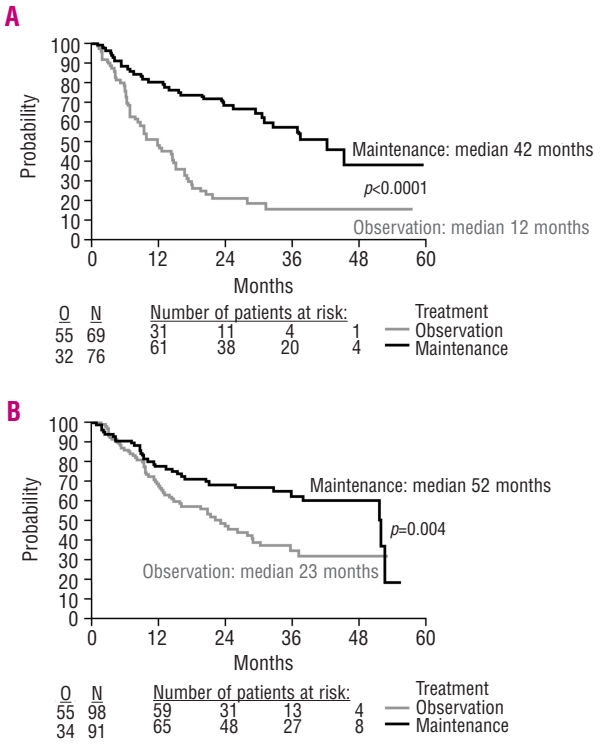

Figure 4. Progression-free survival after rituximab maintenance therapy or observation only in patients with relapsed/refractory follicular lymphoma responding to induction therapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (A) and rituximab plus CHOP (B): EORTC 20891 Intergroup trial.[21]

Rituximab maintenance after ASCT

Another treatment option for younger, high-risk patients with relapsed indolent NHL is high-dose therapy (HDT) and autologous stem cell transplantation (ASCT). Preliminary data from several studies have shown rituximab maintenance therapy after ASCT to be associated with prolonged clinical and molecular remissions, both in patients with FL[25–27] and MCL.[25,28] More recently, the efficacy and safety of rituximab maintenance therapy administered once monthly after HDT and autologous peripheral blood stem cell transplantation (PBSCT) were retrospectively analyzed in 27 patients with NHL treated at a single institution.[29] Of these 27 patients, 15 had indolent NHL (12 FL, 3 immunocytoma) and 12 had aggressive NHL (7 diffuse large B cell lymphoma [DLBCL], 1 Burkitt's lymphoma, 1 mediastinal large cell B cell lymphoma, 3 MCL). Prolonged rituximab maintenance (median 10 months) was well tolerated after HDT and ASCT — 37% of patients developed grade 3/4 hematologic toxicity, the number of minor infections was small and, except for 2 cases of cutaneous varicellar zoster infections, no serious infectious complications occurred. All 12 patients with FL and 4 out of 12 with aggressive NHL were in CR at the time of transplantation. The subset of 12 patients with FL was monitored for minimal residual disease (MRD) in the peripheral blood and bone marrow. It is interesting that 3 patients with FL who were MRD-positive before rituximab maintenance converted to MRD negativity after a median of 12 months of maintenance therapy; seven patients who were MRD-negative before rituximab remained MRD negative on completion of maintenance therapy. After a median follow-up period of 30 months, all 12 patients in the FL subgroup were still alive and, except for 1 patient who transformed from indolent to aggressive disease, there have been no relapses. Overall, this retrospective analysis demonstrates that monthly rituximab infusions administered as maintenance therapy after HDT and autologous PBSCT are feasible, well tolerated, and warrant further investigation as a strategy for post-transplant eradication of MRD, with the aim of prolonging remission duration and OS.

Rituximab maintenance therapy: important unanswered questions

In the studies discussed above, a number of different rituximab maintenance schedules have been explored, ranging from a single rituximab infusion every 3 months for up to 2 years, to once-weekly rituximab infusions for 4 weeks repeated every 6 months for up to 2 years. These schedules, established in the late 1990s, were based both on the pharmacokinetic (PK) data obtained during the pivotal Phase II trial of ritux-

imab 375 mg/m^2 administered once weekly for four doses in patients with relapsed/refractory indolent NHL,[30] and on the observed duration (6–9 months) of rituximab-induced on B cell depletion.[12] In a more recent PK study, patients without progressive disease after a standard course of rituximab subsequently received single infusions of rituximab when the serum level of the drug fell to <25 μg/mL, (i.e. the level considered to be the minimum required for clinical activity of rituximab).[31] For the first rituximab infusion, the median time to next infusion was 5 months (range 1–9 months). For the second and third infusions, the median times to the next infusion were 3.5 months (range 2–5 months) and 3 months (range 2–4 months). Ninety-five percent of patients required three or fewer doses of rituximab in the 12-month follow up period in order to continuously maintain their serum rituximab levels above 25 μg/mL.[31] However, the level of 25 μg/mL has been chosen rather arbitrarily. To date, there are no data demonstrating the optimal rituximab serum level for maintenance therapy. Therefore, results of large, randomised trials comparing different rituximab maintenance schedules would be useful to help establish the best rituximab dosing schedule. However, all maintenance schedules have been shown to be effective. Therefore, the most important question relates to optimal duration of rituximab maintenance treatment. Should this schedule be the maximum period that has been shown to be both effective and safe (i.e. 2 years), or should rituximab maintenance therapy be continued until relapse? Currently available evidence seems to show that extended rituximab dosing is safe in the vast majority of patients studied. However, follow-up times are still relatively short for most studies and there have been isolated reports of patients developing late-onset neutropenia,[32] *Pneumocystis carinii* pneumonia,[33] and activating cutaneous squamous cell carcinoma[34] after rituximab therapy. Therefore, patients must be carefully monitored to confirm the safety of rituximab maintenance therapy. Other important questions also remain. The effect of extended rituximab maintenance treatment on immunoglobulin levels and infection rates, on the incidence of histologic transformation, and on the selection for CD20-negative relapses, must all bel clarified. Furthermore, the optimal treatment for relapses occurring during or shortly after maintenance treatment and the impact on prognosis must be explored. All these questions need to be addressed in ongoing and future prospective trials.

Planned and ongoing studies

The benefits of rituximab maintenance therapy demonstrated in the clinical trials discussed above have led to the adoption of rituximab maintenance therapy as standard in upcoming trials. A number of prospective randomized trials have recently started to further investigate the safety and efficacy of rituximab maintenance therapy and the optimal duration of therapy in patients with FL. These trials are summarized in Table 1.

Summary and conclusions

There is now much evidence that, for patients with FL, the administration of rituximab maintenance after induction therapy prolongs the duration of remission, both in patients with previously untreated and relapsed/refractory disease, and can extend OS. It has also been shown that rituximab maintenance therapy can be safely administered for periods of up to 2 years.

The combination of rituximab and chemotherapy is becoming a widely used standard induction regimen for patients with previously untreated or relapsed/refractory indolent NHL.[23,35–38] Importantly, two trials in relapsed patients have shown that even the excellent responses achieved after rituximab-containing immunochemotherapy induction may be optimized with subsequent rituximab maintenance.[21,24] Results of the PRIMA study on rituximab maintenance after immunochemotherapy in previously untreated patients are eagerly awaited.

For patients unwilling or unable to receive chemotherapy, induction therapy with rituximab alone is an attractive alternative. In responding patients, rituximab maintenance therapy has also been shown to extend the duration of remissions. Also, compared with rituximab retreatment at disease progression, the maintenance approach is associated with a clear improvement in CR rates, significantly longer continuous remissions, and significantly longer PFS.[18]

Various rituximab maintenance schedules have been explored and all demonstrate clear benefits. However, the optimal dose, schedule, and, probably the most important, the duration of maintenance therapy (i.e. for 2 years or until relapse) have not yet been established.

Importantly, from the patient's point of view, rituximab maintenance prolongs the period in which they are free from disease-related symptoms, are able to lead a relatively normal daily life, and can resume or continue working. Furthermore, maintenance treatment may help to avoid the feeling of *passively* waiting for relapse. These aspects of quality of life are key elements in the cost-effectiveness analyses of rituximab maintenance in FL and should be assessed in future trials.

Conflict of Interest

The author has received lectures fees from F. Hoffmann-La Roche.

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