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Maintaining life in indolent lymphoma – from evidence-based medicine to clinical practice

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A B S T R A C T

Patients with indolent non-Hodgkin's lymphoma (NHL) respond well to initial treatment, but relapses are expected and, with sequential recurrences, the quality and durability of responses diminish. The introduction of CD20 antibody therapy has provided a unique and effective new treatment and promising improvements in patient outcomes are now being observed in large-scale clinical trials in combination with standard therapy.

When cure is not attainable, an important goal of therapy is to prolong periods of symptom-free remission after successful induction treatment. A substantial body of evidence now shows that rituximab-based induction therapy for patients requiring treatment improves response rates, quality of response and time to progression, and, in some studies, survival. Because of its efficacy, tolerability and convenient administration, rituximab is also an excellent candidate for maintenance therapy. Efficacy and safety data in relapsed indolent lymphoma from the European Organisation for Research and Treatment of Cancer (EORTC) 20981 and German low-grade lymphoma study group (GLSG) trials will be examined, which support the use of rituximab maintenance therapy to sustain remission.

Rituximab is well tolerated and associated side effects generally have been easily managed and reversible. However, practical and theoretical considerations pertinent to the use of maintenance therapy in indolent lymphoma, such as immunosuppression, must be evaluated and based on available knowledge and evidence. The introduction of rituximab in induction and in maintenance therapy represents progress in the treatment of indolent NHL patients, who now have better prospects of achieving more durable disease control.

Introduction

Indolent non-Hodgkin's lymphoma (NHL) is characterised by a clinical course in which patients respond to treatment but follow a chronically relapsing course, eventually succumbing to progressive or histologically transformed disease. Follicular lymphoma (FL) accounts for approximately 70% of all indolent lymphomas and 22% of all new cases of NHL.[1] A small proportion (20–30%) of patients with FL are diagnosed with stage I or II disease, which can be controlled in the long term and is sometimes cured by involved-field radiation therapy.[2,3] However, most patients present with advanced disease, which is generally considered incurable with current therapies.[1] No standard

first-line systemic therapy for FL had been established as superior to another. In recent years, the introduction of the anti-CD20 monoclonal antibody rituximab has had a major impact on patient outcomes in FL, leading to a new standard of care for patients requiring therapy.

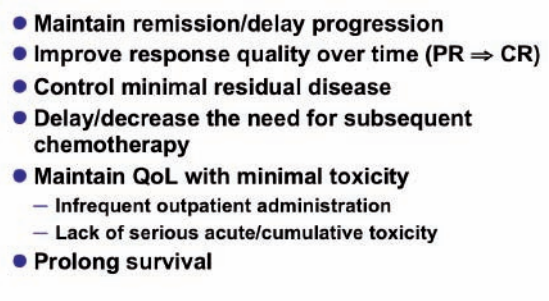

Figure 1: Aims of maintenance treatment in follicular lymphoma

How can patients attain longer remissions in follicular NHL?

Longer remissions would be expected if both a complete clinical response and a 'molecular remission', involving the clearance of cells positive for the t(14;18) or bcl-2 translocation from the blood and bone marrow, are achieved.[4] Molecular remission has been associated with prolonged clinical remission after chemotherapy, high dose therapy and transplantation, and more recently after rituximab-based treatments.[4–10] Even when molecular remission is attained in the blood and marrow, lymphoma cells may persist at other sites or below the level of detection in these compartments. To prolong periods of symptom-free remission after successful induction treatment, a number of therapies have been used to eradicate this residual disease.

Whereas consolidation therapy aims to eradicate malignant cells and secure a high quality remission,[11,12] the concept of maintenance therapy is somewhat different. Maintenance therapy generally involves the continued, regular treatment of patients in remission, in order to prevent the proliferation of malignant cells and therefore maintain remission.[11] In this sense, it may offer the possibility of extended disease control by delaying the need for more intensive treatment. Agents used in maintenance therapy, in addition to having proven efficacy, therefore need to have minimal acute side effects, a low risk of long-term toxicity, convenient administration and should require minimal monitoring of patients (Figure 1). Given these criteria, although efficacious, standard chemotherapy is seldom used for maintenance.[13]

A number of studies have investigated the use of interferon-α as maintenance therapy in lymphoma.[14–19] These studies are difficult to interpret due to differences in patient population, study design and choice of chemotherapy, and dose, schedule and duration of interferon treatment. In the most compelling trial, patients with a high tumour burden received interferon combined with chemotherapy and as maintenance therapy.[15] A meta-analysis including ten Phase III studies and 1,922 patients concluded that interferon-α prolonged survival and remission duration when used above a threshold dose and in the context of relatively intensive induction therapy.[20] A drawback to treatment with interferon-α is its toxicity, which often leads to dose reduction or discontinuation.[21] This fact, coupled with its administration three times per week,[18,21] accounts for the lack of adoption of interferon-α as standard maintenance therapy in FL.

The chimeric monoclonal antibody rituximab binds to the B cell surface antigen CD20[22,23] and has established anti-lymphoma activity as discussed below. Because it specifically targets B cells, other cell types are unaffected and, as a result, the side effect profile is favourable.[11,24] Patients may experience infusion-related

reactions, but these are mostly mild or moderate in nature and often limited to the first infusion.[24] Rituximab is associated with a relative lack of serious acute or cumulative toxicity when administered with or following conventional chemotherapy. However, concerns have arisen as to whether infectious complications will increase during maintenance treatment as a result of long-term B cell depletion. While this has not been shown in randomised clinical trials to date, more data from a larger number of patients is warranted to answer this question. Neutropenia has been reported infrequently with rituximab use. This complication is poorly understood but has generally been seen in patients receiving combination therapy or following intensive chemotherapy.[25,26] Rituximab-related neutropenia has generally resolved spontaneously or after the administration of G-CSF.

An additional advantage of rituximab is that its pharmacokinetic profile affords intermittent dosing measured in months.[11] Although dosing schedules have varied in clinical trials to date, attempts have been made to investigate the optimal interval between administrations. In order to maintain a target level for maintenance therapy, set at 25 μg/mL based on results of the pivotal trial, investigators in one study found the median time required until the first infusion was 5 months (range 1–9 months), the interval to the second infusion was 3.5 months (range 2–5 months) and the third interval was 3 months (range 2–4 months).[27] These data, though limited, provide support for administration of rituximab every 2–3 months. The mechanism of action which underlies rituximab's anti-lymphoma activity may be multifaceted. Rituximab induces both complement-mediated and cell-mediated cytotoxicity, and also initiates apoptosis directly as well as sensitising cells to the apoptotic effects of other agents.[11,22] Whether rituximab acts in synergy with chemotherapy or is purely additive is unclear.[28]

Induction regimen	Outcome (median)		Overall survival	
CHVP ± R + IFN-α[1]	EFS	NR vs 3 yrs $p < 0.0001$	3.5 yr	91% vs 84% $p = 0.029$
MCP ± R[2]	PFS	NR vs 29 mo $p < 0.0001$	4 yr	87% vs 74% $p = 0.0096$
CHOP ± R[3]	TTF	NR vs 31 mo $p = 0.0006$	2 yr	95% vs 90% $p = 0.016$
CVP ± R[4]	TTP	34 mo vs 15 mo $p < 0.0001$	4 yr	83% vs 77% $p = 0.0290$

Figure 2: Phase III trials of rituximab-based induction treatment in previously untreated patients with indolent non-Hodgkin's lymphoma (*Foussard C, et al. J Clin Oncol 2006; 24: Abstract 7508. Herold M, et al. J Clin Oncol 2007; April 9 (Epub). Hiddemann W, et al. Blood 2005; 106:3725–3732. Marcus R, et al. Blood 2006; 108:Abstract 481*).

Having established a rationale for using rituximab as maintenance therapy in indolent NHL, how can its efficacy and safety be assessed? Both disease-related parameters, such as duration of response, progression-free survival (PFS) and overall survival (OS), and patient-related parameters, such as tolerability and quality of life data, should inform evaluations of maintenance therapy.

Achieving quality remission in indolent lymphoma: results with rituximab-based regimens

Four Phase III trials have been published in which rituximab was incorporated into chemotherapy regimens administered to previously untreated patients with indolent NHL and a protocol-defined indication for treatment (Figure 2).

In the first of these studies, 321 patients with FL were randomised to receive treatment with rituximab plus cyclophosphamide, vincristine and prednisolone (R-CVP) or CVP alone.[29] The overall response rate (ORR) was 81% for R-CVP compared with 57% for CVP alone ($p < 0.0001$), and patients receiving R-CVP had a higher proportion of complete responses (CR; 41% versus 10%; $p < 0.0001$).[29] After a median follow-up of 30 months, R-CVP

significantly improved the primary endpoint of time to treatment failure compared with CVP (27 months versus 7 months, respectively; $p < 0.0001$). R-CVP also significantly improved time to progression (TTP) compared with CVP (median 32 months versus 15 months, respectively; $p < 0.0001$).[29] The incorporation of rituximab to the CVP regimen significantly improved TTP regardless of patients' Follicular Lymphoma International Prognostic Index (FLIPI) score, the presence of bulky disease or B-symptoms, and histological grading.[30] In a recent update, R-CVP significantly prolonged OS compared with CVP alone ($p = 0.03$; hazard ratio [HR]: 0.60, 95% confidence interval: 0.38–0.96).[31] The safety profile of R-CVP was favourable and broadly similar to that of CVP, although a higher incidence of infusion-related events was seen in the rituximab arm. The incidence of grade 3/4 neutropenia was higher in the R-CVP group than in the CVP group (24% and 14%, respectively), but there was no difference between groups in the overall infection rate, nor in the incidence of neutropenic sepsis.[29]

The German low-grade lymphoma study group (GLSG) showed that induction therapy, prior to consolidation with interferon or autologous transplantation, with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) improved ORR and CR compared with CHOP (ORR: 96% and 90%, $p = 0.011$; CR: 21% and 17%, p = not significant, respectively) in patients with advanced FL and a protocol-specified indication for treatment.[32] Although the median observation time of 18 months (range 1–38 months) was relatively short, R-CHOP plus interferon or autologous transplant significantly prolonged OS compared with CHOP plus interferon or autologous transplant ($p = 0.016$).[32] A subgroup analysis of 221 elderly patients (> 60 years) showed an estimated 4-year PFS of 62.2% and 27.9% ($p < 0.0001$) and an estimated 4-year OS of 90% and 81% ($p = 0.039$) for the R-CHOP plus interferon and CHOP plus interferon arms, respectively.[33] Treatment-related side effects, key considerations when treating elderly patients, were similar across both treatment groups.[33]

The third study included 358 patients with advanced indolent NHL and mantle cell lymphoma (MCL) who were treated with rituximab plus mitoxantrone, chlorambucil and prednisolone (R-MCP) plus interferon or MCP plus interferon.[34] A median 47-month follow-up in a subset of patients with FL (n = 201) demonstrated that R-MCP substantially improved all endpoints, doubling the CR rate compared with MCP (ORR: 92.4% versus 75%, $p = 0.0004$; CR: 49.5% versus 25%, $p = 0.0009$; median PFS: not reached versus 29 months, $p < 0.0001$).[34] Significantly, there was a survival advantage with R-MCP plus interferon over MCP plus interferon (4-year OS: 87% versus 74%, $p = 0.0096$).[34] Again, rituximab plus MCP did not increase the risk of infections compared with the MCP arm.[34]

The FL2000 study assessed the efficacy of 12 cycles of cyclophosphamide, doxorubicin, teniposide and prednisolone (CHVP) and 18 months of interferon-α compared with 6 cycles of CHVP plus six infusions of rituximab and 18 months of interferon-α in 359 patients with stage II–IV FL and a high tumour burden.[35] After 18 months, patients who received rituximab had a higher CR rate than those in the control arm (CR + CR unconfirmed: 79% versus 63%; partial response: 5% versus 10%), despite a reduction in the overall number of cycles of chemotherapy in the rituximab-containing arm.[35] After a median follow-up of 3.5 years, median event-free survival (EFS) was 3 years in the control group, but not yet reached in the rituximab arm; 46% and 67% of patients remained event-free in each arm, respectively ($p < 0.0001$).[36] In the same analysis, OS was 91% in the rituximab arm and 84% in the control

arm (p = 0.029). Notably, patients in the R-CHVP arm only received half the number of CHVP cycles as control patients.[36]

Taken together, the above studies provide strong evidence that rituximab-based induction therapy improves the quality and duration of remission and extends OS in indolent NHL patients requiring treatment. The benefits of rituximab plus chemotherapy (R-Chemo) were observed across all FLIPI risk groups, although the results in high-risk patients (FLIPI 3–5) were inferior to those obtained in low/intermediate-risk patients (FLIPI 0–2) in all studies where this was assessed.

A Cochrane meta-analysis was performed encompassing seven trials with a total of 1,943 patients with both untreated and relapsed FL or MCL. Analysis of 1,480 patients with FL revealed that rituximab-based induction therapy significantly improved ORR compared with chemotherapy alone ($p < 0.001$); OS was also significantly higher with R-Chemo ($p < 0.001$). Furthermore, collation of toxicity data concluded that although fever and leucocytopenia were increased with rituximab-based induction treatment, this was not associated with an increased risk of infection.[37]

Recent data indicate that, as with chemotherapy or high-dose steroids, reactivation of hepatitis B may occur with rituximab use.[38] These reports may be confounded by co-administration of cytotoxic chemotherapy and also by the underlying disease state. Nonetheless, screening of patients at risk, monitoring of patients with evidence of past infection, and consideration of prophylaxis for selected patients at increased risk of reactivation should be incorporated into clinical practice where appropriate. Furthermore, rare cases of progressive multifocal leucoencephalopathy have been reported among patients treated with rituximab for NHL, primarily in settings of significant immunosuppression.[39–42]

Overall, these studies demonstrated that R-Chemo has become the new standard treatment for indolent lymphoma patients who are symptomatic or otherwise require treatment.[4,43] Questions remain, however, regarding the optimal choice of chemotherapy in different disease settings, the use of maintenance therapy, the role of stem cell transplantation, and the best trial designs for the incorporation of newly available agents.

Maintaining remission in indolent lymphoma – building an evidence base

As discussed earlier, rituximab is perhaps the most suitable currently available candidate for use as monotherapy in maintenance. Data supporting the original approval of rituximab for treating relapsed or refractory FL showed that rituximab monotherapy, administered once weekly at 375 mg/m^2 four times, was associated with a response rate of 48% (CR: 6%), and at 11.8 months the projected median TTP was 13 months.[44]

Proof of concept of rituximab maintenance therapy has so far been confirmed in five large-scale prospective trials.[45–49]

All have demonstrated that rituximab maintenance therapy significantly increased the duration of remission achieved with induction treatment using either single-agent rituximab, chemotherapy or immunochemotherapy.

In the Swiss Group for Clinical Cancer Research (SAKK) 35/98 study in patients with newly diagnosed (n = 64) or relapsed/refractory (n = 138) FL, Ghielmini *et al*. showed that, in previously untreated patients, responders to rituximab induction who received four subsequent rituximab infusions every 2 months had longer EFS than responders who underwent observation only (36 months and 19 months, $p = 0.009$).[45] In the entire study group, rituximab maintenance treatment also increased overall EFS compared with observation only

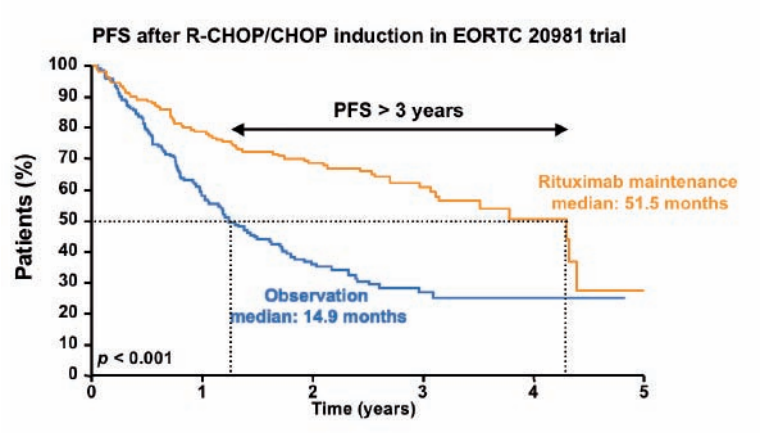

Figure 3: Data from the EORTC 20981 trial show that rituximab maintenance treatment significantly prolongs progression-free survival compared with observation only. (*This research was originally published in Blood. van Oers M, et al. Blood 2006; 108:3296–3301 © the American Society of Hematology*).

(23 months and 12 months, p = 0.02).[45] Hainsworth *et al*. performed a similar study in untreated patients with indolent lymphoma, using rituximab maintenance at 6-month intervals for 2 years.[48] They concluded that rituximab maintenance therapy considerably improved the median actuarial PFS (34 months) compared with the standard 4-week induction treatment alone. Moreover, response rates and duration were similar in subgroups of patients with FL or small lymphocytic lymphoma.[48]

Rituximab maintenance after chemotherapy was first studied in untreated patients in the Eastern Cooperative Oncology Group (ECOG) 1496 study.[46] Rituximab was given to responding or stable patients at four weekly infusions every 6 months for 2 years after CVP induction.[46] Median PFS after randomisation to maintenance or observation arms was 4.2 years and 1.5 years, respectively (p < 0.001). The advantage of rituximab maintenance treatment was greatest in those patients who had a high initial tumour burden and minimal residual disease after CVP. Similar outcomes were separately reported for the subset of 237 patients with FL treated in this study; in this subgroup, median PFS was 5.1 years for patients receiving maintenance rituximab versus 1.3 years for those under observation (p < 0.001).[46]

In the relapsed setting, the European Organisation for Research and Treatment of Cancer (EORTC) 20981 trial evaluated the efficacy of rituximab combined with CHOP compared with CHOP alone as induction therapy in 465 patients with relapsed/refractory FL.[47] R-CHOP significantly increased response rates and median PFS compared with CHOP (ORR: 85.1% and 72.3%, p < 0.001; CR: 29.5% and 15.6%, p < 0.001; median PFS: 33.1 months and 20.2 months, p < 0.001; HR for R-CHOP: 0.65). The trial went on to compare the efficacy of rituximab maintenance therapy (one infusion every 3 months for a maximum of 2 years) compared with observation.[47] A significant increase in PFS was seen with maintenance rituximab compared with the observation arm (51.5 months versus 14.9 months; HR: 0.40, p < 0.001; Figure 3).[47] The increase in PFS was observed both after CHOP induction (median PFS: 42.2 months versus 11.6 months; HR: 0.30, p < 0.001) and after R-CHOP induction (median PFS: 51.8 months versus 23.0 months; HR: 0.54, p = 0.004). OS was also extended in the total patient group (R-CHOP or CHOP induction; 85.1% versus 77.1% at 3 years, respectively; HR: 0.52, p < 0.011; Figure 4) for those patients receiving rituximab maintenance compared with those under observation.[47] It will be important to assess this approach in untreated patients (see below).

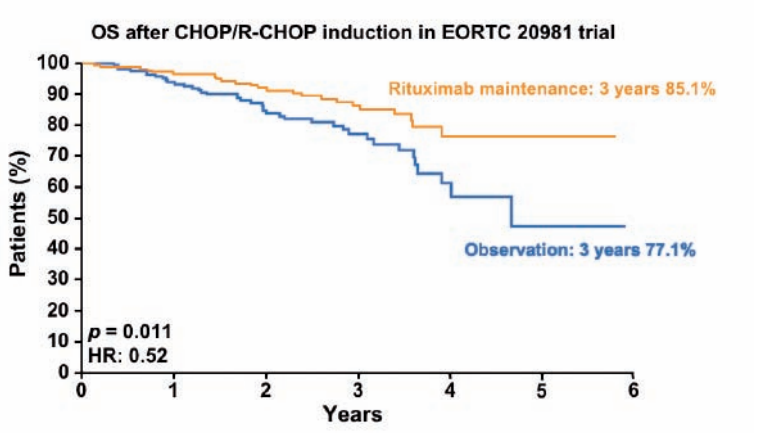

Figure 4: Data from the EORTC 20981 trial show that rituximab maintenance treatment significantly extends overall survival compared with observation only. (*This research was originally published in Blood. van Oers M, et al. Blood 2006; 108:3296–3301 © the American Society of Hematology*).

The GLSG study included 147 patients with relapsed/refractory FL or MCL treated with fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without rituximab.[50] Subgroup analyses showed that R-FCM improved ORR in patients with FL (94% versus 70%, p = 0.011) and prolonged PFS compared with control (median 16 months versus 10 months; p = 0.0381).[50] After completion of induction therapy, responders were randomised to rituximab maintenance or observation.[49] After a median 26-month follow-up, rituximab maintenance therapy significantly prolonged the duration of response compared with observation only (not reached versus 17 months; p < 0.001).[49] In a subset analysis with very modest patient numbers, the benefit of rituximab maintenance was retained in R-FCM patients with FL (p = 0.035 for rituximab maintenance compared with observation).[49] Estimated OS at 3 years was 77% after rituximab maintenance and 57% with observation only (p = 0.100).[49]

In addition to the studies of maintenance rituximab versus observation listed above, Hainsworth *et al*. performed a randomised Phase II trial in 114 patients with FL or small lymphocytic lymphoma who had received previous chemotherapy but had progressive disease.[51] All patients were treated with a standard 4-week course of rituximab, and those with an objective response or stable disease were randomised to maintenance rituximab (one course every 6 months for 2 years) or rituximab re-treatment at the time of progression. The primary endpoint was a measure of 'duration of rituximab benefit', defined as the time until another treatment modality was required. This endpoint was comparable in both treatment arms (31.3 months and 27.4 months, p = not significant).[51] At a median follow-up of 41 months, the median PFS for the maintenance group was 31.3 months, compared with 7.4 months in the re-treatment group (p = 0.007).[51] One drawback of the trial is that those who completed treatment in the maintenance arm and later relapsed were not eligible for re-treatment with rituximab, although this is an option in clinical practice as discussed further below.

Rituximab-based maintenance therapy has been generally well tolerated when administered for up to 2 years. When rituximab maintenance was used as primary therapy in the ECOG 1496 study, no significant difference was observed in the incidence of neutropenia and infection between rituximab-based maintenance therapy and observation groups.[46] In the EORTC 20981 study of recurrent disease, the only adverse events that occurred significantly more with

rituximab maintenance therapy were neutropenia and grade 3/4 infections (mainly ear, nose and throat), and these were manageable and reversible.[47] During 2 years of maintenance therapy, fewer than 4% of patients discontinued treatment because of rituximab-associated toxicity and there were no deaths related to rituximab maintenance.[47] In the GLSG study in patients with recurrent disease, rituximab maintenance therapy was similarly well tolerated: no significant differences were noted in the infection rate, nor in other side effects, between the rituximab maintenance and observation arms.[49] Infusion-related side effects occurred in 8% of maintenance cycles but were mild to moderate in nature.[49]

Based on the results of the EORTC 20981 study, rituximab was licensed for maintenance therapy in relapsed/refractory patients in the European Union and elsewhere in the summer of 2006. Also in 2006, maintenance rituximab was approved after induction chemotherapy with CVP in the United States in untreated patients. The data examined above, derived from patients who relapsed after or were refractory to chemotherapy, serve as the basis for the use of rituximab-based maintenance therapy as a standard of care for patients (aged ≥ 18 years) with relapsed FL who respond to second-line induction therapy. The extended period of remission achieved by employing rituximab maintenance therapy, which reached 3 years in the EORTC trial, is likely to delay subsequent therapies and may contribute to an improved quality of life.

Maintenance therapy in practice

The studies discussed above established that R-Chemo achieves superior response, TTP and OS in patients with indolent lymphoma who require treatment. Prolonged PFS was observed with rituximab maintenance after chemotherapy in the primary setting, and the benefit of maintenance rituximab in the context of recurrent disease has been demonstrated. As a result, the major question that emerges is the use of rituximab in both induction and maintenance strategies in the primary setting. This is addressed by the recently accrued Primary Rituximab and Maintenance (PRIMA) study. In PRIMA, patients with untreated advanced FL were treated with eight cycles of rituximab plus CVP, CHOP or FCM as induction. Responders were subsequently randomly assigned to rituximab maintenance, administered every 2 months for 2 years, or observation only. The primary endpoint of the study is PFS, and follow-up will continue for 5 years after the end of treatment (Figure 5).

If the PRIMA study demonstrates that rituximab maintenance is beneficial and well tolerated, a number of additional questions emerge. These include identifying the optimal chemotherapy for induction and the optimal schedule and duration for maintenance therapy. Several ongoing trials conducted in Europe and North America will shed light on these issues. A related question concerns the length of time between completing induction therapy and initiating maintenance therapy. Prospective studies have shown that rituximab maintenance treatment is effective when initiated up to 6 months after induction therapy, but no direct comparisons have been made so far.[45–49]

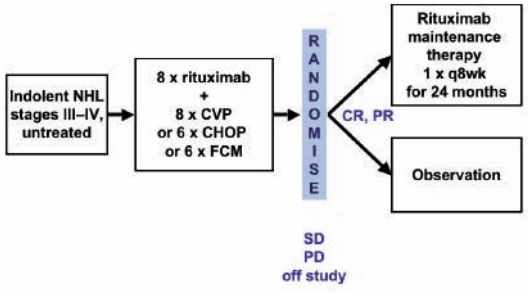

Figure 5: PRIMA study design

In the context of maintenance treatment, safety concerns become paramount. An increased rate of grade 3/4 infections has been observed during maintenance, many of which can be managed using antibiotics as appropriate. Prophylactic antibiotic treatment is not indicated. Patients may also experience neutropenia, which is usually resolved by temporarily interrupting rituximab maintenance therapy or administering growth factor treatment. There may also be implications for vaccinations such as influenza; an ongoing European study is investigating the efficacy of influenza vaccinations as a function of decreasing IgM levels, but no data are available as yet. Consideration of the effects of long-term depletion of B cells with rituximab maintenance therapy may also be required during clinical practice. Because rituximab does not deplete the CD20-stem cells in the bone marrow, levels of B cells are usually replenished within a year of the last rituximab infusion.[52–54] No significant clinical consequences have been associated with B-cell depletion in randomised trials to date, although changes in immunoglobulin (Ig) levels have occurred.[45,47] At the second randomisation in the EORTC 20981 study, the median IgG level was just below the normal range in both treatment arms (observation arm: 6.6 g/L, maintenance arm: 6.5 g/L). During 2 years of observation only, IgG levels rose to within the normal range (7.3 g/L); with rituximab maintenance therapy, they remained stable (6.3 g/L). However, maintenance was delayed or omitted in only three patients due to persistently low IgG levels, and no withdrawals occurred. The majority of low IgG levels were in fact observed following induction (~4.5% of responders were ineligible for second randomisation).[47] Furthermore, recent evidence shows that, out of all B cells, the levels of circulating Ig-secreting cells recover first during rituximab maintenance treatment (administered every 2 months), and were detectable in absolute numbers similar to those observed in healthy donors.[55] Human naive and memory B cells were detected in peripheral blood 4–6 months after therapy.[55] In the SAKK trial, levels of IgM but not IgG were below normal limits. No association with infection was observed.[45]

Lastly, is re-treatment with rituximab an effective option? Phase II data from re-treated patients showed a 40% response rate with no apparent difference from initial exposure in response duration or adverse effects.[56] Hainsworth *et al*. obtained long-term follow-up data (median 7 years) from patients who had received 2 years of rituximab maintenance therapy.[57] Of 24 patients who progressed and received single-agent rituximab as next therapy, 8 had a complete or partial response and 14 had stable disease; median PFS in these 22 patients was 47 months, with 27% of patients progression-free at 5 years.[57] Thus a significant proportion of patients who are re-treated with rituximab remain sensitive to its anti-lymphoma effects, some with enduring clinical benefits.

Based on these observations, a study by SAKK is comparing rituximab induction therapy followed by either short-term maintenance (one infusion every 2 months, four times) or extended maintenance (one infusion every 2 months until relapse, up to 5 years). In addition, the ECOG 4402 (RESORT) trial is underway in newly diagnosed patients with stage III/IV indolent NHL with a low tumour burden. Its aim is to evaluate the time until rituximab resistance is observed in patients responsive to initial rituximab monotherapy, who are then randomised to receive either rituximab maintenance therapy every 3 months until disease progression or rituximab re-treatment (375 mg/m^2 weekly for 4 weeks) at disease progression. This will allow the efficacy of an extended rituximab treatment schedule to be compared with re-treatment as needed. Both the SAKK and RESORT studies address the optimal use of rituximab monotherapy as maintenance treatment.

Conclusions

The efficacy and safety data discussed above demonstrate the extent of progress made over recent years in treating follicular lymphoma with the novel anti-CD20 monoclonal antibody rituximab. Substantial evidence now exists for rituximab use in combination with chemotherapy as induction for untreated patients with an indication for treatment. Maintenance therapy has been associated with prolonged remissions in a variety of settings, including after R-Chemo in relapsed disease, and data from the PRIMA trial, which addresses the efficacy and safety of maintenance following R-Chemo in the primary setting, are eagerly awaited. There is also evidence for using rituximab-based induction and maintenance therapy in the relapsed setting for at least rituximab-naive patients. Patients with indolent lymphoma who now require therapy have better prospects for achieving successful induction and durable remissions than before, benefiting from an evidence base derived from authoritative Phase III clinical trials.

References

1. Evans LS & Hancock BW. Non-Hodgkin lymphoma. Lancet 2003; 362:139–146.
2. Tsang RW & Gospodarowicz MK. Radiation therapy for localized low-grade non-Hodgkin's lymphomas. Hematol Oncol 2005; 23:10–17.
3. Vaughan HB, Vaughan HG, MacLennan KA, et al. Clinical stage 1 non-Hodgkin's lymphoma: long-term follow-up of patients treated by the British National Lymphoma Investigation with radiotherapy alone as initial therapy. Br J Cancer 1994; 69:1088–1093.
4. Czuczman MS. Controversies in follicular lymphoma: "who, what, when, where, and why?" (not necessarily in that order!). Hematology Am Soc Hematol Educ Program 2006; 303–310.
5. Colombat P, Salles G, Brousse N, et al. Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation. Blood 2001; 97:101–106.
6. Chang CC, Bredeson C, Juckett M, et al. Tumor load in patients with follicular lymphoma post stem cell transplantation may correlate with clinical course. Bone Marrow Transplant 2003; 32:287–291.
7. Gribben JG, Neuberg D, Freedman AS, et al. Detection by polymerase chain reaction of residual cells with the bcl-2 translocation is associated with increased risk of relapse after autologous bone marrow transplantation for B-cell lymphoma. Blood 1993; 81:3449–3457.
8. Pott C, Schrader C, Gesk S, et al. Quantitative assessment of molecular remission after high-dose therapy with autologous stem cell transplantation predicts long-term remission in mantle cell lymphoma. Blood 2006; 107:2271–2278.
9. Ladetto M, de Marco F, Benedetti F, et al. Clinical and molecular results of the multicenter randomized GITMO-IIL trial in poor risk follicular lymphoma (FL) at diagnosis: rituximab-supplemented high-dose sequential chemotherapy (R-HDS) is superior to CHOP-R in molecular remissions rate, EFS and PFS. ASH Annual Meeting Abstracts 2006; 108:325.
10. Colombat P, Brousse N, Morschhauser F, et al. Single treatment with rituximab monotherapy for low-tumour burden follicular lymphoma (FL): survival analyses with extended follow-up (F/Up) of 7 years. Blood 2006; 108: Abstract 486.
11. Berinstein NL. Principles of maintenance therapy. Leuk Res 2006; 30 (suppl 1):S3–10.
12. Zinzani PL, Pulsoni A, Perrotti A, et al. Fludarabine plus mitoxantrone with and without rituximab versus CHOP with and without rituximab as front-line treatment for patients with follicular lymphoma. J Clin Oncol 2004; 22:2654–2661.
13. Ghielmini M. Patient benefits of maintenance immunotherapy. Leuk Res 2006; 30 Suppl 1:S22–S26.
14. Aviles A, Neri N, Huerta-Guzman J, et al. Interferon alpha 2b as maintenance therapy improves outcome in follicular lymphoma. Leuk Lymphoma 2004; 45: 2247–2251.
15. Solal-Celigny P, Lepage E, Brousse N, et al. Recombinant interferon alfa-2b combined with a regimen containing doxorubicin in patients with advanced follicular lymphoma. Groupe d'Etude des Lymphomes de l'Adulte. N Engl J Med 1993; 329:1608–1614.
16. Hiddemann W, Griesinger F & Unterhalt M. Interferon alfa for the treatment of follicular lymphomas. Cancer J Sci Am 1998; 4:S13–S18.
17. Lynch JW, Hei DL, Braylan RC, et al. Phase II study of fludarabine combined with interferon-alpha-2a followed by maintenance therapy with interferon-alpha-2a in patients with low-grade non-hodgkin's lymphoma. Am J Clin Oncol 2002; 25:391–397.
18. Rohatiner A, Radford J, Deakin D, et al. A randomized controlled trial to evaluate the role of interferon as initial and maintenance therapy in patients with follicular lymphoma. Br J Cancer 2001; 85:29–35.
19. Salles GA, Foussard C, Mounier N, et al. Rituximab added {alpha}IFN+CHVP improves the outcome of follicular lymphoma patients with a high tumor burden: to first analysis of the GELA-GOELAMS FL-2000 randomized trial in 359 patients. ASH Annual Meeting Abstracts 2004; 104:160.
20. Rohatiner AZ, Gregory WM, Peterson B, et al. Meta-

analysis to evaluate the role of interferon in follicular lymphoma. J Clin Oncol 2005; 23:2215–2223.
21. Solal-Celigny P, Lepage E, Brousse N, et al. Doxorubicin-containing regimen with or without interferon alfa-2b for advanced follicular lymphomas: final analysis of survival and toxicity in the Groupe d'Etude des Lymphomes Folliculaires 86 Trial. J Clin Oncol 1998; 16:2332–2338.
22. Cartron G, Watier H, Golay J, et al. From the bench to the bedside: ways to improve rituximab efficacy. Blood 2004; 104:2635–2642.
23. Reff ME, Carner K, Chambers KS, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. Blood 1994; 83:435–445.
24. Kimby E. Tolerability and safety of rituximab (MabThera). Cancer Treat Rev 2005; 31:456–473.
25. Cattaneo C, Spedini P, Casari S, et al. Delayed-onset peripheral blood cytopenia after rituximab: frequency and risk factor assessment in a consecutive series of 77 treatments. Leuk Lymphoma 2006; 47:1013–1017.
26. McLaughlin P. Late-onset neutropenia following rituximab. Leuk Lymphoma 2006; 47:965–966.
27. Gordan LN, Grow WB, Pusateri A, et al. Phase II trial of individualized rituximab dosing for patients with CD20-positive lymphoproliferative disorders. J Clin Oncol 2005; 23:1096–1102.
28. Ghielmini M. Multimodality therapies and optimal schedule of antibodies: rituximab in lymphoma as an example. Hematology (Am Soc Hematol Educ Program) 2005; 321–328.
29. Marcus R, Imrie K, Belch A, et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005; 105:1417–1423.
30. Imrie K, Belch A, Pettengell R, et al. Rituximab plus CVP chemotherapy vs CVP alone as first-line treatment for follicular lymphoma: treatment effect according to baseline prognostic factors. American Society of Clinical Oncology. Orlando; 2005; Abstract 6525.
31. Marcus RE, Solal-Celigny P, Imrie K, et al. MabThera (rituximab) plus cyclophosphamide, vincristine and prednisone (CVP) chemotherapy improves survival in previously untreated patients with advanced follicular non-Hodgkin's lymphoma (NHL). Blood 2006; 108: Abstract 481.
32. Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005; 106: 3725–3732.
33. Buske C, Kneba M, Lengfelder E, et al. Front-Line combined immuno-chemotherapy (R-CHOP) significantly improves the time to treatment failure and overall survival in elderly patients with advanced stage follicular lymphoma - results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG). ASH Annual Meeting Abstracts 2006; 108:482.
34. Herold M, Haas A, Srock S, et al. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interfon maintenance prolongs survival in patients with advanced follicular lymphoma: an East German Study Group Hematology and Oncology study. J Clin Oncol 2007; Apr 9, Epub ahead of print.
35. Salles G, Foussard C, Mounier N, et al. Rituximab added to alpha-IFN+CHVP improves the outcome of follicular lymphoma patients with a high tumor burden: first analysis of the GELA-GOELAMS FL-2000 randomized trial in 359 patients. Blood 2004; 104:Abstract 160.
36. Foussard C, Mounier N, Van Hoof A, et al. Update of the FL2000 randomized trial combining rituximab to CHVP-Interferon in follicular lymphoma (FL) patients (pts). J Clin Oncol 2006; 24:Abstract 7508.
37. Schulz H, Bohlius J, Skoetz N, et al. Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst 2007; 99:706-714.
38. Hanbali A, Khaled Y, Ajrouche H, et al. Incidence of Hepatitis B Reactivation in Association with Rituximab Therapy. ASH Annual Meeting Abstracts 2006; 108: 2766.
39. Freim Wahl SG, Folvik MR & Torp SH. Progressive multifocal leukoencephalopathy in a lymphoma patient with complete remission after treatment with cytostatics and rituximab: case report and review of the literature. Clin Neuropathol 2007; 26:68–73.
40. Steurer M, Clausen J, Gotwald T, et al. Progressive multifocal leukoencephalopathy after allogeneic stem cell transplantation and posttransplantation rituximab. Transplantation 2003; 76:435–436.
41. Matteucci P, Magni M, Di Nicola M, et al. Leukoencephalopathy and papovavirus infection after treatment with chemotherapy and anti-CD20 monoclonal antibody. Blood 2002; 100:1104–1105.
42. Goldberg SL, Pecora AL, Alter RS, et al. Unusual viral infections (progressive multifocal leukoencephalopathy and cytomegalovirus disease) after high-dose chemotherapy with autologous blood stem cell rescue and peritransplantation rituximab. Blood 2002; 99:1486–1488.
43. Horning SJ. Natural history of and therapy for the indolent non-Hodgkin's lymphomas. Semin Oncol 1993; 20: 75–88.
44. McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol 1998; 16:2825–2833.
45. Ghielmini M, Schmitz SF, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood 2004; 103:4416–4423.
46. Hochster HS, Weller E, Gascoyne RD, et al. Maintenance rituximab after CVP results in superior clinical outcome in advanced follicular lymphoma (FL): Results of the E1496 Phase III trial from the Eastern Cooperative Oncology Group and the Cancer and

Leukemia Group B. Blood 2005; 106:Abstract 349.
47. van Oers MH, Klasa R, Marcus RE, et al. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin's lymphoma, both in patients with and without rituximab during induction: results of a prospective randomized phase III intergroup trial. Blood 2006; 108:3295–3301.
48. Hainsworth JD, Litchy S, Burris HA, III, et al. Rituximab as first-line and maintenance therapy for patients with indolent non-hodgkin's lymphoma. J Clin Oncol 2002; 20:4261–4267.
49. Forstpointner R, Unterhalt M, Dreyling M, et al. Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006; 108:4003–4008.
50. Forstpointner R, Dreyling M, Repp R, et al. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2004; 104: 3064–3071.
51. Hainsworth JD, Litchy S, Shaffer DW, et al. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma--a randomized phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol 2005; 23:1088–1095.
52. Maloney DG. Mechanism of action of rituximab. Anticancer Drugs 2001; 12 (suppl 2):S1–S4.
53. Ghielmini M, Rufibach K, Salles G, et al. Single agent rituximab in patients with follicular or mantle cell lymphoma: clinical and biological factors that are predictive of response and event-free survival as well as the effect of rituximab on the immune system: a study of the Swiss Group for Clinical Cancer Research (SAKK). Ann Oncol 2005; 16:1675–1682.
54. Edwards JC & Cambridge G. B-cell targeting in rheumatoid arthritis and other autoimmune diseases. Nat Rev Immunol 2006; 6:394–403.
55. Wirths S, Ruprecht C, Bertoni F, et al. Hierarchy of human B cell regeneration after rituximab therapy. Blood 2006; 108:Abstract 936.
56. Davis TA, Grillo-Lopez AJ, White CA, et al. Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: safety and efficacy of re-treatment. J Clin Oncol 2000; 18:3135–3143.
57. Hainsworth JD, Meng C, Spigel DR, et al. Long-Term Follow-up of Patients with Follicular Lymphoma (FL) Treated with Two Years of Maintenance Rituximab: Response to Rituximab Retreatment at Progression. Blood 2006; 108:Abstract 4723.