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

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.

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. Molecular remission has been associated with prolonged clinical remission after chemotherapy, high dose therapy and transplantation, and more recently after rituximab-based treatments. 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, 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. 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.

A number of studies have investigated the use of interferon-α as maintenance therapy in lymphoma. 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. 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. A drawback to treatment with interferon-α is its toxicity, which often leads to dose reduction or discontinuation. This fact, coupled with its administration three times per week, 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 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. 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

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

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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). 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. 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). 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.

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. 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). 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. Treatment-related side effects,
key considerations when treating elderly
patients, were similar across both treatment
groups.

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. 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). Significantly, there was a survival
advantage with R-MCP plus interferon over
MCP plus interferon (4-year OS: 87% versus
74%, p = 0.0096). Again, rituximab plus MCP
did not increase the risk of infections compared
with the MCP arm.

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. 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.
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-containing arm (p < 0.0001). 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.\textsuperscript{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.\textsuperscript{37}

Recent data indicate that, as with chemotherapy or high-dose steroids, reactivation of hepatitis B may occur with rituximab use.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{44}

Proof of concept of rituximab maintenance therapy has so far been confirmed in five large-scale prospective trials.\textsuperscript{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, Ghelmini \textit{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).\textsuperscript{45} In the entire study group, rituximab maintenance treatment also increased overall EFS compared with observation only.
Hainsworth et al. performed a similar study in untreated patients with indolent lymphoma, using rituximab maintenance at 6-month intervals for 2 years. 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.

Rituximab maintenance after chemotherapy was first studied in untreated patients in the Eastern Cooperative Oncology Group (ECOG) 1496 study. Rituximab was given to responding or stable patients at four weekly infusions every 6 months for 2 years after CVP induction. 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).

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. 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. 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). 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. It will be important to assess this approach in untreated patients (see below).
The GLSG study included 147 patients with relapsed/refractory FL or MCL treated with fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without rituximab. 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). After completion of induction therapy, responders were randomised to rituximab maintenance or observation. 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). 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). Estimated OS at 3 years was 77% after rituximab maintenance and 57% with observation only (p = 0.100).

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. 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). 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). 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. 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. 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. 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. Infusion-related side effects occurred in 8% of maintenance cycles but were mild to moderate in nature.

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.
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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{45} 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.\textsuperscript{55} Human naive and memory B cells were detected in peripheral blood 4–6 months after therapy.\textsuperscript{53} In the SAKK trial, levels of IgM but not IgG were below normal limits. No association with infection was observed.\textsuperscript{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.\textsuperscript{46} Hainsworth \textit{et al.} obtained long-term follow-up data (median 7 years) from patients who had received 2 years of rituximab maintenance therapy.\textsuperscript{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.\textsuperscript{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\textsuperscript{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.

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