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Rituximab therapy for indolent non-Hodgkin's lymphoma

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Indolent non-Hodgkin's lymphomas (NHLs) are essentially incurable with current treatments. Rituximab is a specific anti-CD20 chimeric monoclonal antibody against the CD20 antigen, which is stably expressed on most B-cells (from the pre-B-cell stage). Compared with chemotherapy, rituximab has an excellent tolerability profile, making it a good therapeutic option for patients with indolent NHL. In the pivotal study for rituximab, patients with relapsed or refractory indolent or follicular lymphoma (FL) had an overall response rate of 50%. There is evidence that first-line rituximab therapy may be associated with better response rates; in previously untreated FL with a low tumor burden, rituximab monotherapy has produced an overall response rate of 73%. Attempts to improve response rates to rituximab by increasing the dose or frequency of dosing showed that the addition of four extra infusions of rituximab (in addition to the standard treatment schedule) resulted in an overall response rate of 76% in patients with FL. Augmenting rituximab with cytokines is also an option for increasing response rates in patients with indolent NHL. In a trial by the Nordic Lymphoma Study Group in patients with previously untreated or first-relapse indolent NHL, who had stable disease or a partial response after four doses of rituximab, 48% of the patients treated with rituximab plus interferon-α2a achieved a complete response. A further option is to combine rituximab with chemotherapy. Interim analyses from the East German Study Group have shown that rituximab plus mitoxantrone, chlorambucil and prednisolone (MCP) resulted in overall response rates of 89% in patients with untreated indolent lymphoma. Rituximab is therefore an excellent treatment option both as first-line and as salvage therapy for patients with indolent NHL. [© 2002 Lippincott Williams & Wilkins.]

Key words: rituximab, indolent non-Hodgkin's lymphoma, cytokine, immunochemotherapy.

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Introduction

Indolent non-Hodgkin's lymphomas (NHLs) represent approximately 35–40% of new NHL cases and are characterized by a slowly progressive, continually relapsing course with ever-decreasing periods of remission.[1,2] Follicular lymphoma (FL) is the most common type of indolent NHL, and comprises approximately 20% of all NHL cases reported in Europe and the USA.[1]

There are several treatment options for indolent NHL, but none are curative and the median survival is 8–10 years from the time of diagnosis. Chemotherapy, such as treatment with chlorambucil or cyclophosphamide, vincristine and prednisone (CVP), can be associated with response rates of up to 80% in patients with indolent NHL. However, chemotherapy has not been shown to improve overall survival.[3]

The failure of conventional therapy in the treatment of indolent NHL has led to a number of trials of high-dose chemotherapy with autologous stem-cell transplantation (ASCT).[4] Recent studies have shown that this combination may offer the chance of longer progression-free survival, particularly in the younger patient.[5] Nevertheless, improved treatments for indolent NHL remain an urgent clinical need.

Rituximab is a human/mouse chimeric anti-CD20 monoclonal antibody that targets the CD20 antigen, which is stably and exclusively expressed on more than 95% of B-cells. Compared with chemotherapy, rituximab displays an excellent tolerability profile, making it a good treatment option for indolent NHL. This article reviews the current state of knowledge regarding the efficacy of rituximab, either as a monotherapy or in combination with other agents, in the treatment of indolent NHL.

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Rituximab monotherapy

The efficacy of rituximab in relapsed indolent NHL is well established. In the pivotal study of 166 patients with relapsed and refractory low-grade or follicular NHL, four once-weekly infusions of rituximab (375 mg/m^2) resulted in an overall response (OR) rate of 48%.[6] In addition, the *bcl-2* gene rearrangement, a characteristic marker of FL, was effectively cleared from the peripheral blood of patients treated with rituximab (Figure 1).[6,7] Absence of *bcl-2* was correlated with higher response rates and a statistically significant improvement in the duration of response (Table 1). Rituximab treatment was well tolerated. The majority of adverse events (grade 1/2 fever and chills) occurred during the first infusion only, and grade 3/4 adverse events were observed in only a minority of patients. At the time this study was carried out, a complete response (CR) was defined as the resolution of all symptoms and signs of lymphoma, including clearing of the bone marrow for at least 28 days. Since then, however, the response criteria in NHL have been revised and have been applied retrospectively to the rituximab pivotal study.[8,9] Using revised response criteria, the OR rate in this trial has been demonstrated to be 56% (32% CR) (Figure 2), and updated results show long-term durable remissions in 20% of responders.[10]

Studies of rituximab monotherapy in previously untreated patients suggest that response rates may be somewhat higher than in relapsed or refractory patients. Hainsworth *et al.*[11] reported response rates of 52% for rituximab used as a first-line treatment in patients with indolent NHL, including patients with small lymphocytic lymphoma (SLL). Relapsed patients with SLL had a response rate of only 12% in the pivotal study.[6]

Rituximab demonstrated excellent efficacy as a first-line treatment in 50 previously untreated FL patients with a low tumor burden.[12] In this study, the overall response rate, one month after treatment with four weekly rituximab infusions (375 mg/m^2), was 73%, with at least 20% of the patients in complete remission and 46% in partial remission. In addition, 57% of the patients were demonstrated to be polymerase chain reaction (PCR)-negative for the *bcl-2* gene rearrangement in peripheral blood one month after the start of rituximab. At 12 months' follow-up, 62% of the patients were PCR-negative, and the molecular response was shown to correlate with progression-free survival.

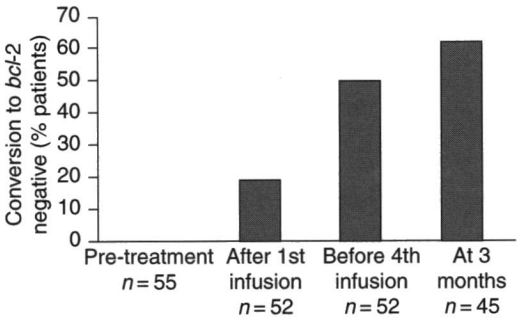

Figure 1. Clearance of *bcl-2* from the peripheral blood of patients treated with four infusions of rituximab. Reproduced with permission from McLaughlin *et al.*[6]

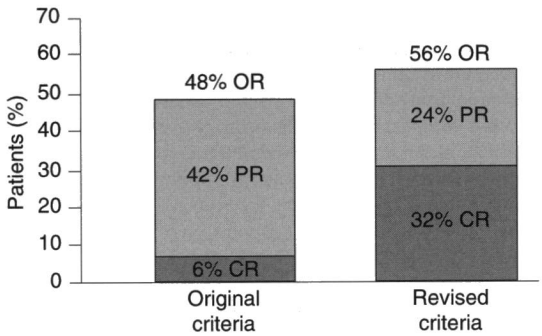

Figure 2. Response rates to rituximab monotherapy according to the original and the revised criteria. OR, overall response; PR, partial response; CR, complete response. Reproduced with permission from Grillo-Lopez *et al.*[9]

Table 1. Effect of *bcl-2* clearance on response rate in patients with relapsed or refractory indolent non-Hodgkin's Lymphomas: the pivotal study

	OR (%)	CR (%)	PR (%)	Median TTP (months)
Bcl-2 negative	72	11	61	19
Bcl-2 positive	31	0	31	9
P value	0.018			0.006

OR, overall response; CR, complete response; PR, partial response; TTP, time to progression.

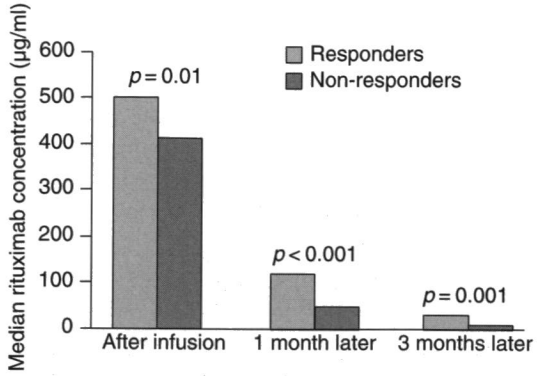

Figure 3. Correlation of response rate with serum rituximab concentration. Reproduced with permission from Berinstein *et al.*[13]

Improving the response to rituximab: increasing the dose and frequency

Although it has been demonstrated that rituximab has efficacy in indolent NHL, the CR rate could be improved, and the majority of patients will relapse. A number of approaches to improving the response rates have been suggested. In recurrent FL it has been noted that patients with good responses tended to have high serum concentrations of rituximab (Figure 3).[13] This observation has led to a number of studies investigating the effect of increasing the dose or dosing frequency of rituximab in those patients who do not respond well to standard dosing regimens. Recent studies have shown that increasing the dose of rituximab and/or the frequency of treatment can improve response rates in patients with chronic lymphocytic leukemia (CLL) with no associated increase in toxicity.[14,15] In a study in relapsed or refractory indolent NHL, patients were treated with eight consecutive weekly doses of rituximab monotherapy, which resulted in an OR rate of 60% in evaluable patients.[16]

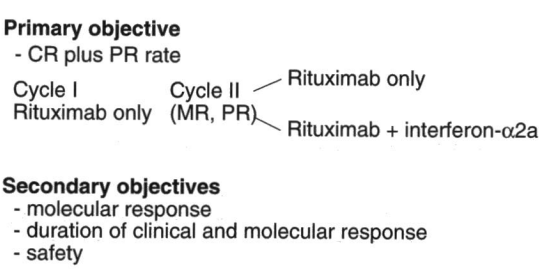

Figure 4. Treatment schedule of the Nordic Lymphoma Group in symptomatic patients with indolent non-Hodgkin's lymphoma. CR, complete response; PR, partial response; MR, minor response.

The Swiss Group for Clinical Research (SAKK) 35/98 trial has been initiated to investigate the efficacy of different treatment schedules in patients with untreated or relapsed FL or mantle cell lymphoma (MCL). In this study, patients were given a standard course of rituximab (375 mg/m^2) once a week for 4 weeks. Those patients who responded or had stable disease following rituximab treatment were randomized to either maintenance therapy, with a further infusion of rituximab every 2 months for four infusions, or to observation. Data from this trial are yet to be published.

Augmentation with cytokines

Cytokines such as interferon-α (IFN-α) and granulocyte colony-stimulating factor (G-CSF) have known immune-modulating effects, including the activation of natural killer effector cells and enhancing the cytotoxicity of neutrophils in antibody-dependent cytotoxicity.[17–19] These immunological agents therefore have potential for improving the response to rituximab treatment. *In vitro*, IFN-α has been shown to upregulate the CD20 antigen on B-cells taken from patients with CLL, suggesting that priming with IFN-α may augment the effectiveness of antibody therapy.[20] The combination of G-CSF with rituximab has also been assessed. In a phase I/II study, patients with relapsed indolent NHL received the standard dose of rituximab for 4 weeks in combination with a subcutaneous dose of G-CSF. Although the response rate (42%) was comparable to that reported for rituximab monotherapy, the duration of remission was remarkably long, with the median duration of response not reached at a median follow-up of 23 months.[21]

In an attempt to improve the response in those patients who have a suboptimal response to rituximab monotherapy, the Nordic Lymphoma Study Group has evaluated the efficacy of co-administrating rituximab and IFN-α2a in symptomatic patients with indolent NHL.[22] A total of 127 patients (126 intent-to-treat patients) with previously untreated or first-relapse indolent NHL were given four infusions of rituximab monotherapy. Those with partial or minor responses (69 patients) were then randomized to a further four cycles of rituximab, with or without IFN-α2a. A schematic representation of the treatment schedule is shown in Figure 4. Four further infusions of rituximab plus IFN-α2a resulted in a CR rate of 48%, whereas treatment with four further rituximab infusions

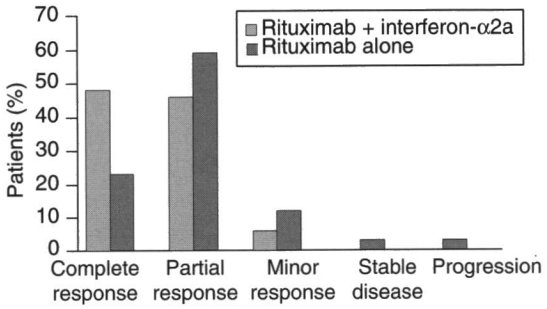

Figure 5. Augmentation of the complete response rate with co-administration of rituximab and interferon-α2a.

alone resulted in a CR rate of 23% (Figure 5). Both treatments were well tolerated. An analysis of CD20 expression on lymphoma cells at baseline was performed. No clear correlation was found between response and the density of the CD20 antigen on cells (from lymph node biopsies). CRs were observed after the first and second infusions of rituximab (with or without IFN-α2a) in patients with both high and low baseline CD20 density. In order to investigate whether there was an effect of IFN-α on CD20 density, cells were studied before and after IFN treatment. However, due to previous rituximab treatment, too few $CD20^+$ cells could be analyzed.

In another study of IFN-α plus rituximab in patients with relapsed low-grade NHL, four infusions of the standard dose of rituximab were given after priming and simultaneous treatment with IFN-α2a. An OR rate of 70% was demonstrated, with a median duration of response of 19 months.[23]

These studies suggest that the IFN-α may augment the effectiveness of rituximab therapy. Further studies are required to identify which patients are most likely to benefit from the addition of cytokines to rituximab treatment.

Rituximab combination therapy: immunochemotherapy

Rituximab has a different mode of action to chemotherapy and has non-overlapping toxicity, allowing the combination of these two therapies (immunochemotherapy) to become an attractive treatment option.

Immunochemotherapy may offer an effective regimen in indolent NHL. In the first report demonstrating the efficacy and safety of rituximab in combination with chemotherapy in low-grade or follicular NHL, 40 patients with untreated or relapsed disease received six infusions of the standard dose of rituximab plus six courses of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). In the intent-to-treat population, an excellent OR rate (95%) was demonstrated, with 55% of the patients experiencing a CR (Table 2).[24] At a median follow-up of 29 months, 74% of the evaluable patients were in complete remission.[24] In a phase II study in previously treated or untreated indolent NHL, seven standard doses of rituximab were given in combination with six cycles of fludarabine. An initial response rate of 92% was observed, with the median duration of response not reached at 15+ months.[25]

To confirm these excellent results, the outcome of ongoing randomized studies of immunochemotherapy versus chemotherapy alone in indolent NHL are eagerly awaited. The German Low Grade Study Group has initiated a prospective, randomized, multicentre trial comparing rituximab plus fludarabine, cyclophosphamide and mitoxantrone (R-FCM) to FCM alone, in patients with FL, MCL or immunocytoma who had relapsed following CHOP chemotherapy (Figure 6). The OR rate for patients treated with R-FCM (89%) was significantly better than that for patients treated with FCM alone (53%) (Table 3). Response rates were shown to be independent of the age of the patient and the number of previous

Table 2. Response to rituximab plus CHOP in patients with untreated or relapsed indolent non-Hodgkin's lymphoma. Reproduced with permission from Czuczman *et al.*[24]

Patient group	*n*	CR (%)	PR (%)	CR + PR (%)
Intent-to-treat	40	55	40	95
Extranodal disease	29	52	48	100
Elevated LDH	11	45	55	100
Bone marrow involvement	22	50	50	100
Age ⩾60 years	11	45	55	100
Bulky disease[a]	14	29	71	100

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; LDH, lactate dehydrogenase; CR, complete response; PR, partial response.

[a]Patients with a lesion ⩾5 cm (but no more than 10 cm) in the largest diameter.

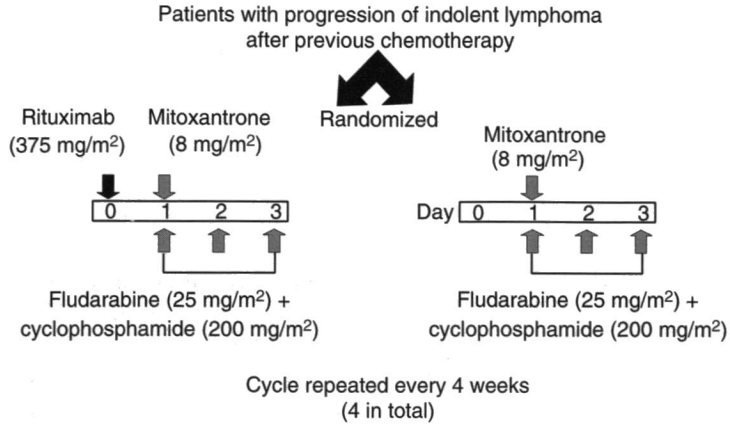

Figure 6. Schedule for the rituximab plus fludarabine, cyclophosphamide and mitoxantrone combination therapy trial of the German Low Grade Study Group.

treatments. R-FCM was also well tolerated by elderly patients. There were no significant differences in the safety profile between the two treatment arms.[26]

The very high response rates and long duration of remission seen in the phase II studies with immunochemotherapy suggest that rituximab plus chemotherapy may also represent a good first-line treatment option for indolent NHL. To assess this, the East German Study Group is currently conducting a phase III prospective, randomized, multicenter trial comparing the efficacy and safety of rituximab plus MCP (mitoxantrone, chlorambucil and prednisolone) with MCP alone, in patients with advanced FL, immunocytoma or MCL (Figure 7). Although data for efficacy are yet unblinded, an interim analysis of 106 evaluable patients (55 in the rituximab plus MCP group and 51 in the MCP group) has shown an OR rate of 81% (CR rate 40%) for all patients. Adverse events were similar between the two groups and were mainly attributed to the chemotherapy. Adverse

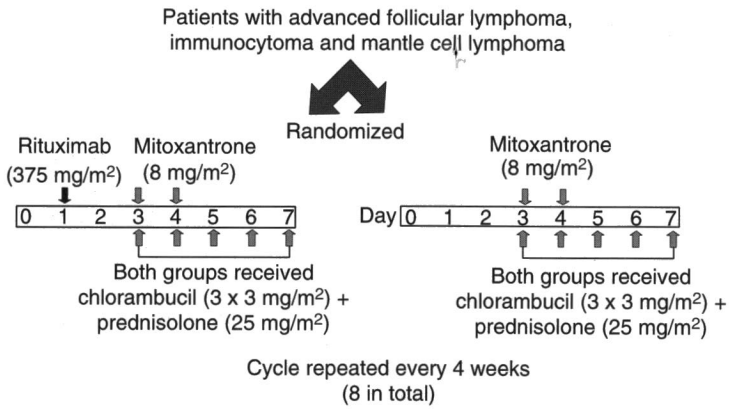

Figure 7. Schedule for the rituximab plus mitoxantrone, chlorambucil and prednisolone combination therapy trial of the East German Study Group.

Table 3. OR rates for rituximab plus fludarabine, cyclophosphamide and mitoxantrone (R-FCM) and FCM alone in patients with relapsed or refractory indolent NHL in the German Low Grade Study Group trial

	R-FCM (%)	FCM (%)
All patients ($n = 80$)	89	53
Follicular lymphoma ($n = 43$)	95	68
Mantle cell lymphoma ($n = 27$)	77	27

events attributed to rituximab consisted primarily of infusion-related reactions, although more cases of grade 4 leukopenia were observed in the rituximab group (13% of cycles versus 6%, $p = 0.008$).[27] Final analyses will provide data on response rates, time to treatment failure, overall survival and disease-free survival in the two treatment groups. The German Low Grade Study Group also has a study underway comparing CHOP with rituximab plus CHOP. The results from these ongoing studies of immunochemotherapy will show whether there may be a cure for patients with indolent NHL; very long follow-up periods will be required to confirm this.

Discussion

Improving outcomes in indolent NHL remains a challenge, and progress in progression-free survival, time to next treatment and overall survival is essential. As monotherapy, rituximab offers an effective and well-tolerated treatment for indolent NHL. An important consideration in the choice of treatment for patients with incurable disease is the toxicity profile of the therapy and the subsequent impact on quality of life. The efficacy and good tolerability, together with the short treatment schedule of rituximab monotherapy (completed within 4 weeks), makes this treatment an excellent therapeutic choice for patients with indolent NHL. Furthermore, owing to their unique mechanism of action, monoclonal antibodies are good candidates for augmentation by other (chemo)therapies or immunological agents. Immunochemotherapy has yielded very high response rates and has been shown to produce prolonged durations of remission. Especially good response rates have been reported for immunochemotherapy as a first-line therapy. Randomized studies are underway to determine if immunochemotherapy confers a survival advantage. It has already been demonstrated that response rates may be further improved by increasing the intensity or frequency of dose, and the use of cytokines to prime or augment the effector response of the immune system is a promising addition to the rituximab strategy against NHL.

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