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Rituximab In Indolent Lymphomas

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Abstract

Indolent Non Hodgkin's lymphoma (NHL) comprises a group of incurable, generally slow growing lymphomas highly responsive to initial therapy with a relapsing and progressive course. Rituximab, an anti CD-20 antibody, has had a large impact on treatment of indolent NHL. Its effectiveness as a single agent and in conjunction with known chemotherapy regimens has made it a standard of care in the treatment of NHL. Analysis of data obtained from NHL clinical trials as well as data from the National Cancer Institute indicates that the overall survival of indolent NHL has improved since the discovery of rituximab. Given its effectiveness and tolerability, it is currently being investigated as a maintenance agent with encouraging results. This review summarizes several landmark trials utilizing rituximab as a single agent and in combination with chemotherapy for treatment of NHL. In addition, a review of the studied rituximab maintenance dosing schedules and its impact on NHL will also be presented. Overall, rituximab has changed the landscape for treatment of indolent NHL however additional research is necessary to identify the optimal dosing schedule as well as patients most likely to respond to prolonged rituximab therapy.

Introduction

Indolent Non-Hodgkin's lymphoma (NHL) represents a group of incurable slow growing lymphomas that are highly responsive to initial therapy but relapse with less responsive disease.[1-4] The landscape for treatment of indolent NHL has dramatically changed with the introduction of rituximab (Rituxan, Genetech, San Francisco, CA). Its greatest impact has been in follicular lymphoma (FL), which constitutes approximately 70% of indolent lymphomas and up to 25% of all cases of NHL.[5,6] Although there are no defined first line therapies for indolent NHL, rituximab has become a standard component in treatment of FL.[7] While indolent lymphoma remains an incurable disease, recent data from the Surveillance Epidemiology and End Results (SEER) database and retrospective analysis of clinical trials in indolent NHL suggest an improved overall survival (OS) with the use of rituximab (Figure 1).[8-10] It is hoped that overall survival can be further improved with the use of extended rituximab dosing schedules.

Follicular Lymphoma – Rituximab Monotherapy

The initial trials investigating rituximab for treatment of FL was as a single agent. In a pivotal trial conducted by McLaughlin *et al.*[11], 166 patients with heavily treated relapsed low grade lymphoma including 136 with follicular lymphoma were given rituximab 375mg/m^2 weekly

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for four doses. Of the patients enrolled, 48% responded with a median time to progression (TTP) of 13.0 months among responders.[11] Toxicity was mild and greatest during the first infusion without development of treatment related cytopenias. Compared to single agent cytotoxic therapy, single agent rituximab was better tolerated and had similar efficacy.[11]

Rituximab monotherapy has significant clinical activity in previously untreated patients as well. A trial of fifty patients with newly diagnosed stage II/III/IV FL received rituximab 375mg/m^2 weekly for four doses. Patients were required to have a low tumor burden defined as an absence of bulky lymphadenopathy, B symptoms, significant splenomegaly and normal serum LDH.[12] The observed response rate was 73% four weeks following completion of therapy.[12] Polymerase chain reaction (PCR) analysis of BCL-2 rearrangement was performed pre and post therapy as well. Long term follow-up revealed a median PFS of 37 months for patients who became BCL-2 negative following therapy as compared to 12 months for those who remained BCL-2 positive[13] suggesting that patients with a molecular response to rituximab have a more indolent course.

Rituximab monotherapy has also been evaluated in combination with other forms of immunotherapy. Using patient-specific B-cell immunoglobulin idiotypes, a therapeutic vaccine can be created which in theory can produce a durable clinical response. This was tested in a randomized clinical trial of 364 patients with follicular lymphoma, the majority of which were treatment naïve. All patients were treated with rituximab 375mg/m^2 weekly for four weeks. Those with an objective response were then randomized to receive a vaccine or placebo. Treatment naïve patients who were randomized to receive a vaccine had a TTP of 11.9 months as compared to 17.2 months in the placebo arm ($P = 0.258$).[14] Patients with relapsed disease had a TTP of 6.0 months in the vaccine arm as compared to 11.2 months for the placebo arm ($P = 0.004$).[14] The authors concluded that the difference in TTP among patients with relapsed disease is related to an imbalance in FLIPI risk scores among both treatment arms. While a negative vaccine effect cannot be excluded, when adjusting for FLIPI risk score, there was no significant difference in TTP for those with relapsed disease. Although addition of a patient-specific vaccine did not improve TTP, results of this trial highlight the effectiveness of single agent rituximab in follicular lymphoma and support the results seen in the aforementioned trials.

Follicular Lymphoma – Single Agent Rituximab Maintenance

The concept of maintenance chemotherapy is a recurrent theme in oncology that dates back decades from experience in the curability of acute lymphoblastic leukemia in children. Several studies in indolent lymphoma have attempted to improve OS and PFS in NHL with the use of interferon, chlorambucil and multi-agent chemotherapy with mixed results and a high incidence of adverse effects limiting patient adherence.[15-18] To date, rituximab is the first non-chemotherapy drug that is highly effective without treatment associated cytopenias or severe cumulative toxicity.[19,20] The advent of a well tolerated, effective drug with a favorable pharmacokinetic profile has led to a resurgence in studying maintenance therapy (Table 1).

The first trial of rituximab maintenance by Hainsworth *et al.*[21] was a phase II trial to assess response duration with an extended rituximab schedule. Sixty-two patients (38 FL, 24 CLL) with stage II/III/IV disease were enrolled. The authors also accepted patients with stage I/II disease who had relapsed following prior radiation therapy; however, patients with prior chemotherapy were excluded from this study. Enrolled patients received rituximab 375mg/m^2 weekly for a total of four weeks. Disease response was assessed two weeks following induction and patients with an objective response or stable disease received rituximab 375mg/m^2 weekly for four weeks every 6 months for 24 months.

The addition of a rituximab maintenance schedule led to an improved overall response rate (ORR) such that with continued therapy, 16 of 27 patients (59%) with stable disease achieved an objective response.[21] Median PFS following the addition of prolonged rituximab dosing was 34 months. It is important to note that this analysis contains patients with CLL; however ORR and PFS are not significantly different across NHL subtypes.[21] Prolonged rituximab therapy was well tolerated with few grade 3 or 4 adverse events.

Although Hainsworth demonstrated an improved ORR and progression free survival (PFS) with an extended rituximab schedule, it is unknown whether maintenance therapy is more effective than re-treatment at the time of progression. This was addressed initially in a randomized phase II study where 90 patients (62 with FL) were given rituximab 375mg/m^2 weekly for a total of four doses. Those with an objective response were randomized to maintenance rituximab as in the previously mentioned trial by Hainsworth[21] or rituximab re-treatment at time of progression. For patients with FL, PFS with maintenance rituximab was 31 months versus 13 months with rituximab re-treatment (Figure 2).[22] However, duration of response was similar between both study arms (31vs. 35 months for maintenance and re-treatment, respectively) (Figure 3).[22] Moreover, 3-year survival was not significantly improved in the maintenance arm as compared to the re-treatment arm (72% vs. 68% respectively).[22] The recently completed phase III rituximab extended schedule or re-treatment trial (RESORT) study is hoped to definitively address the benefit of maintenance rituximab as compared to re-treatment at the time of progression.

A similar trial of prolonged rituximab therapy by Ghielmini *et al.*[23] was performed using a different treatment schedule based upon pharmacokinetic data. The goal of this schedule was to maintain a mean rituximab drug level greater than 25.4 mcg/ml, a level which in prior studies was observed in responding patients.[24] In this study, 202 patients with stage I/II/III FL who have not received prior antibody therapy were enrolled to receive rituximab 375mg/m^2 weekly for four weeks. Eight weeks following induction therapy, those with an objective response or stable disease were randomized to receive rituximab 375mg/m^2 every two months for four doses or observation.

Following induction therapy, response rate (RR) was 52% with no significant difference between the study arms. [23] However, the response rate of decline following induction therapy was significantly less pronounced in those randomized to rituximab maintenance 12 months following randomization.[23] Furthermore, patients who achieved CR following induction therapy remained in CR for a greater period of time if randomized to rituximab maintenance (36 vs. 16 mo).[23] Event free survival (EFS) also improved with the addition of a prolonged rituximab dosing schedule. This improvement was greatest in chemotherapy naïve patients (36 vs. 19 mo, $P = 0.009$) and responders (36 vs. 16 mo, $P = 0.004$) as compared to those randomized to observation.[23]

As in their initial report, the Ghielmini extended rituximab dosing schedule did not result in improved event free survival (EFS) in previously treated patients. Subsequent long term follow-up data in abstract form revealed a 5 year EFS of 26% for those randomized to prolonged rituximab dosing as opposed to 10% in the observation arm independent of prior therapy.[25] Whereas initial results indicated that chemotherapy naïve patients had an improved EFS as compared to pretreated patients, long term follow-up does not support this.[25] It is unknown what characteristics predispose a patient to a prolonged EFS thus highlighting the need for continued research in extended rituximab dosing. This is currently underway in a randomized study of rituximab maintenance for 2 years versus 5 years. Thus far, data presented at the 2009 American Society of Clinical Oncology (ASCO) annual meeting did not reveal any safety concerns associated with rituximab maintenance beyond 2 years.[26]

Given the number of available treatment options for follicular lymphoma, it is important to identify patients in whom single agent therapy should be considered. In patients with relapsed or refractory follicular lymphoma, single agent rituximab therapy should be considered when other options cannot be tolerated. Unfortunately, the optimal dosing schedule for single agent therapy remains unknown. Clinical studies are underway to ascertain the optimal dosing schedule as the relapsing nature of indolent lymphoma makes rituximab resistance a valid concern. Although rituximab resistance has been demonstrated in *in vitro* models, rituximab retreatment has been evaluated in clinical trials without any significant loss of treatment effect.[19,27]

Follicular Lymphoma – Rituximab Combined with Chemotherapy

Following the effectiveness of rituximab as a single agent treatment, rituximab was added to frontline combination chemotherapy in an attempt to improve long term outcome. Encouraging results from a phase II study of rituximab combined with cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)[28] prompted five pivotal trials to examine the benefit of adding rituximab to chemotherapy regimens commonly used to treat FL (Table 2). One such trial was a phase III trial that compared R-CHOP to CHOP alone. In this multicenter prospective randomized trial, patients with symptomatic, previously untreated, advanced stage FL, grades I and II were enrolled. Participants were randomized to receive either CHOP or R-CHOP for a total of 6 to 8 cycles. Overall response rates were 96% for R-CHOP versus 90% for CHOP (*P =0.011*).[29] R-CHOP was associated with a significantly improved time to treatment failure (TTF) and a longer duration of response.[29]

Median TTF and response duration were achieved in the CHOP study arm but not in the R-CHOP arm. Therefore, neither TTF nor response duration could be accurately established for the R-CHOP arm in the predetermined follow up period of this study. Treatment related adverse effects were similar among both arms with the exception of increased neutropenia in those receiving R-CHOP. However, this did not lead to an increase in neutropenic infections.[29] Infusion related adverse effects were mild and subsided by the second infusion.

Efforts at obtaining accurate time to progression and duration of response following R-CHOP have led to extended follow up periods. One such follow up of 9 years was conducted following completion of R-CHOP for FL as part of a phase II trial of R-CHOP for indolent NHL. Analysis of the 38 patients with advanced stage FL who received six cycles of R-CHOP revealed a median TTP of 82.3 months with a median duration of response of 83.5 months.[30]

In addition to combining rituximab to CHOP chemotherapy, rituximab was also added to another widely used chemotherapy regimen consisting of cyclophosphamide, vincristine and prednisone (CVP). In this multicenter randomized phase III trial, patients with symptomatic, previously untreated, advanced stage FL grades I to III were randomized to receive R-CVP or CVP (dose of cyclophosphamide only 750mg/m^2) for a maximum of 8 cycles. The response rate for R-CVP was 81% as compared to 57% in the CVP arm (*P <0.0001*) and treatment with R-CVP significantly improved TTF by 20 months (27 mo vs. 7 mo in R-CVP and CVP arms respectively, *P < 0.0001*).[6] Response duration was enhanced with the addition of rituximab to 35 months versus 14 months in the CVP only group.[6] The addition of rituximab was well tolerated with a small number of grade 3 or 4 rituximab related reactions.

In vitro studies of commonly used chemotherapy agents revealed synergism with the addition of rituximab to either prednisone or mitoxantrone.[31,32] This led to the evaluation of mitoxantrone, chlorambucil and prednisone with rituximab (R-MCP). In a study by Herold *et al.*[33], 358 previously untreated, symptomatic patients with indolent NHL (201 with FL) were randomized to R-MCP or MCP for a maximum of 8 cycles. At the completion of therapy, overall response rate (ORR) for those randomized to R-MCP was 92% as compared to 75% in

the MCP arm (*P = 0.0009*).[33] Further analysis revealed that the number of those in CR were twice as great in the R-MCP arm as compared to MCP (*P = 0.0004*).[33] PFS was not reached in the R-MCP arm as compared to 28.8 mo in those randomized to MCP. Although median OS was not reached in either study arm, 4 year survival rates favored R-MCP (87% vs. 74% for R-MCP vs. MCP respectively, *P = 0.0096*).[33] Adverse events were similar among both study arms with the exception of an increase in grade 3 or 4 leukopenia observed in the R-MCP study arm, however this did not lead to an increase in infections.[33]

As there is no consensus in regards to optimal first line therapy for FL, several other regimens have been utilized to a lesser extent in the treatment of FL.[7] One such regimen involves the use of fludarabine and rituximab (FR). Based upon in vitro studies suggesting synergism of this combination[34] and separate mechanisms of action, FR combination therapy was studied in indolent NHL. Forty patients, 31 with histologically confirmed FL, received FR for a total of 6 cycles.

Previously treated patients were enrolled and comprised 33% of the study population. Overall response rate (ORR) following FR was 90% with no significant difference in response according to prior treatment.[35] Despite a median follow-up period of 44 months, response duration, overall survival and time to progression could not be assessed. Grade 3 or 4 neutropenia was common among patients however reversible with G-CSF support. Typical rituximab associated infusion reactions were observed with initial doses as described in previous trials of rituximab.

Treatment of previously treated FL patients can be challenging as there are cumulative dose limitations and adverse effects related to chemotherapy. For patients previously treated with CHOP or CHOP-like regimens, fludarabine based regimens can be used. The addition of rituximab to a fludarabine based regimen was studied by Forstpointner *et al.*[36] in which 147 previously treated patients (72 with FL) were randomized to receive 4 cycles of fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without rituximab (R-FCM). ORR in FL patients randomized to R-FCM was 94% and consisted of 40% CR, 54% PR.[36] Those randomized to FCM experienced an ORR of 70% with 23% CR and 47% PR (*P = 0.011*).[36] R-FCM was superior to FCM irrespective of the number of prior therapies.[36] Median PFS was not reached for those randomized to R-FCM as opposed to 21 months in the FCM study arm.[36] OS was not reached for both arms during the study observation period; however 2 year estimated median OS was 90% for those randomized to R-FCM and 70% for those in the FCM arm (*P = 0.0943*).[36] Perhaps with further observation one would expect this difference to become significant given the significant difference in PFS.

The addition of rituximab to chemotherapy has enhanced response rates and progression free survival in all of the aforementioned trials. Efforts at long term survival analysis have been attempted and although an improved survival is suggested, it is not clearly definitive. Furthermore, sample sizes are small and long term follow up data does not apply for all chemotherapy regimens used in indolent NHL. Data from a recent meta-analysis of immunochemotherapy evaluating 1943 patients revealed a pooled hazard ratio for death of 0.65 (95% CI = 0.54 – 0.78) in favor of immunochemotherapy.[37] When stratified for the 1480 patients with FL, the pooled hazard ratio for mortality was 0.63 (95% CI = 0.51 – 0.79) in favor of immunochemotherapy.[37] Based upon this hazard ratio and an assumed 2 year OS of 90%, the number needed to treat with immunochemotherapy to prevent one death in 2 years is 28.[37]

Rituximab has greatly changed the manner in which indolent NHL is treated. Its application as a single agent has led to an improved PFS with minimal toxicity and has emerged as first line therapy for those unable to tolerate aggressive measures. The addition of rituximab to

chemotherapy has had a clear impact on response rate, PFS and response duration with a suggestion towards improved OS irrespective of the chemotherapy regimen to which it is coupled. The improvement in RR, PFS and duration of response in patients treated with immunochemotherapy makes rituximab the standard of care for FL treatment.

Other Indolent Lymphomas

Lymphoplasmacytic lymphoma (LPL) [Waldenstrom macroglobulinemia (WM)] is an uncommon indolent NHL which as a result is underrepresented in the literature. Use of rituximab in this disease is particularly important as it does not promote cytopenias associated with LPL. This was evaluated by the German Low-Grade Lymphoma Study Group (GLSG) in a phase III trial of 70 previously untreated patients with advanced LPL randomized to R-CHOP vs. CHOP. The addition of rituximab to CHOP resulted in an ORR of 94 vs. 67% and a TTF of 63 vs. 22 months.[38] Treatment was well tolerated without any difference in side effects among study treatment arms.

The combination of rituximab with fludarabine was also evaluated in a recent phase II trial for treatment of LPL.[39] Forty-three patients with FR naïve LPL who had received at most two prior therapies received 8 infusions of rituximab along with 6 cycles of fludarabine. The combination of FR was effective in reducing IgM levels as well as bone marrow involvement with an ORR of 95.3%.[39] Response rates were not significantly different for previously treated versus previously untreated patients. However, TTP was significantly greater in treatment naïve patients, 77.6 months, compared to previously treated patients, 51.2 months.[39] Neutropenia was common necessitating fludarabine dose reduction. IgM flare, a phenomenon by which IgM levels increase following initial dosing of rituximab, was seen in this study although it was uncommon. Data from similar studies of FR in LPL indicated that concurrent immunochemotherapy rather than sequential dosing of FR decreases the potential for rituximab-associated IgM flare.[40]

Similarly, the uncommon nature of marginal zone lymphoma (MZL) has limited the number of dedicated studies on the optimal therapeutic approach. Historically, this subtype of indolent NHL has been studied in conjunction with other more prevalent indolent lymphomas. As a result, treatment of MZL is approached in a similar fashion to treatment of FL with similar results for rituximab monotherapy as well as rituximab based therapies.[41,42]

Maintenance Rituximab Therapy Following Chemotherapy

Prolonged rituximab dosing has also been studied in relapsed FL by Van Oers *et al.*[43] In this study, 465 previously treated patients with advanced stage FL were randomized to R-CHOP versus CHOP for a total of 6 cycles. Those with an objective response were randomized to rituximab 375mg/m^2 every three months for a total of 24 months or observation. Data in abstract form from long term follow-up indicates that patients randomized to prolonged rituximab therapy had a PFS of 3.7 years as compared to 1.3 years in the observation arm.[44] This improvement in PFS was maintained regardless of whether patients received CHOP or R-CHOP during induction.[43,44] Three year OS was also improved by the addition of prolonged rituximab therapy as initially reported (85.1% vs. 77.1%).[43] However, data from long term follow-up revealed a trend towards improved OS with a 5-year OS of 74% for prolonged rituximab dosing versus 64% for observation ($P = 0.07$).[44] One possible explanation for a nonsignificant increase in OS despite a significant increase in PFS is that several patients from both study arms received rituximab monotherapy following disease progression.[44] It should be noted this rituximab-naïve patient population is different from most patients in the United States, and it is inappropriate to extrapolate these results to patients relapsing after rituximab containing chemotherapy regimens.

The role of maintenance rituximab following initial chemotherapy for treatment of naïve patients is unknown. A recent phase III study by Hochester *et al.*[45] evaluated the impact of maintenance rituximab in the upfront setting following non-rituximab containing chemotherapy. In this study, 109 patients with previously untreated FL were given CVP. Those with an objective response or stable disease were then randomized to rituximab 375mg/m^2 weekly for four doses every 6 months for 24 months or observation. Those randomized to maintenance rituximab experienced an improved PFS as compared to the observation arm (4.3 vs. 1.3 yrs).[45] Overall survival however was not improved by the addition of maintenance rituximab; however a subset analysis indicated that patients with a high tumor burden had an improved OS with maintenance rituximab.[45]

Unfortunately, this study did not use rituximab upfront with CVP as is common practice today. At the time this study was conducted, rituximab was not used with chemotherapy in the upfront setting. Since rituximab based chemotherapy is the standard of care for treatment of FL, it is unclear how applicable this study can be given the lack of upfront rituximab. In unusual circumstances where non-rituximab containing regimens have been used, rituximab maintenance should be considered in the relapsed setting if other treatment strategies cannot be employed.

The concept of maintenance rituximab is an appealing treatment option for FL given its efficacy, tolerability and ease of administration. The ability to extend OS has not been proven in long term follow-up although data from the Van Oers study indicates that rituximab naïve patients have an improved PFS with the addition of maintenance rituximab.[43] Perhaps additional follow up is necessary in order to demonstrate a survival benefit. However, if a survival benefit cannot be established in the relapsed setting, it is difficult to expect that an effect will be seen in previously untreated patients, where the TTF is much longer.

It is hoped that the Primary Rituximab and Maintenance (PRIMA) study will address the question of whether to incorporate maintenance rituximab following upfront R-chemotherapy in previously untreated FL. The largest FL trial of its kind, it has accrued over 1000 patients with previously untreated FL and randomized them to maintenance rituximab according to the Ghielmini schedule versus observation following R-chemotherapy. Given its large sample size, this trial should be adequately powered to detect a survival difference. The preliminary results are expected soon.

Future Directions

Despite the successful improvement of disease free intervals with the addition of rituximab maintenance, there are several needed areas of further research. Several groups have attempted to improve efficacy of rituximab with immunostimulants to enhance antibody-dependent cellular cytotoxicity or complement mediated cytotoxicity.[46] Rituximab has been safely combined with IL-2,[47,48] alpha interferon,[49] and IL-12.[50] We[51,52] and others[53] have studied rituximab in combination with TLR-9 agonists, which have pleiotropic immunostimulatory effects. In general, these single arm trials have suggested enhanced progression-free survival when rituximab is combined with immunostimulatory agents compared to historical controls of single agent rituximab. However, randomized studies are required to definitively determine the effect of adding immunostimulants to rituximab, and whether these agents would have a role in combination with chemotherapy.

To date, there have been three published trials of rituximab maintenance, each with a different number of rituximab doses and different duration of therapy. However, all three have similar results thus highlighting a lack of knowledge regarding the optimal rituximab dosing schedule. Long term follow up from the initial study conducted by Ghielmini *et al.* suggests that the effects of rituximab can be long lasting in a certain percentage of patients[25]; however there is

no method by which to identify these patients. Research on host-associated resistance mechanisms to rituximab has identified various polymorphisms of the Fcgamma RIIIA receptor that affect response to rituximab containing regimens in follicular lymphoma, but this has not been validated prospectively.[54,55] Given the cost of rituximab maintenance and potential undetermined long-term risks, a greater emphasis on identification of potential responders as well as an optimal dosing schedule and duration are greatly needed.

In this issue of Seminars in Hematology, there is a chapter on novel anti-CD20 monoclonal antibodies. Many of these antibodies have been engineered to have increased cytotoxicity compared with rituximab. Until superior activity is demonstrated in randomized clinical trials, we feel it is unlikely these antibodies will replace rituximab in the routine treatment of indolent lymphoma. Therefore, continued study of this most valuable therapeutic agent is warranted.

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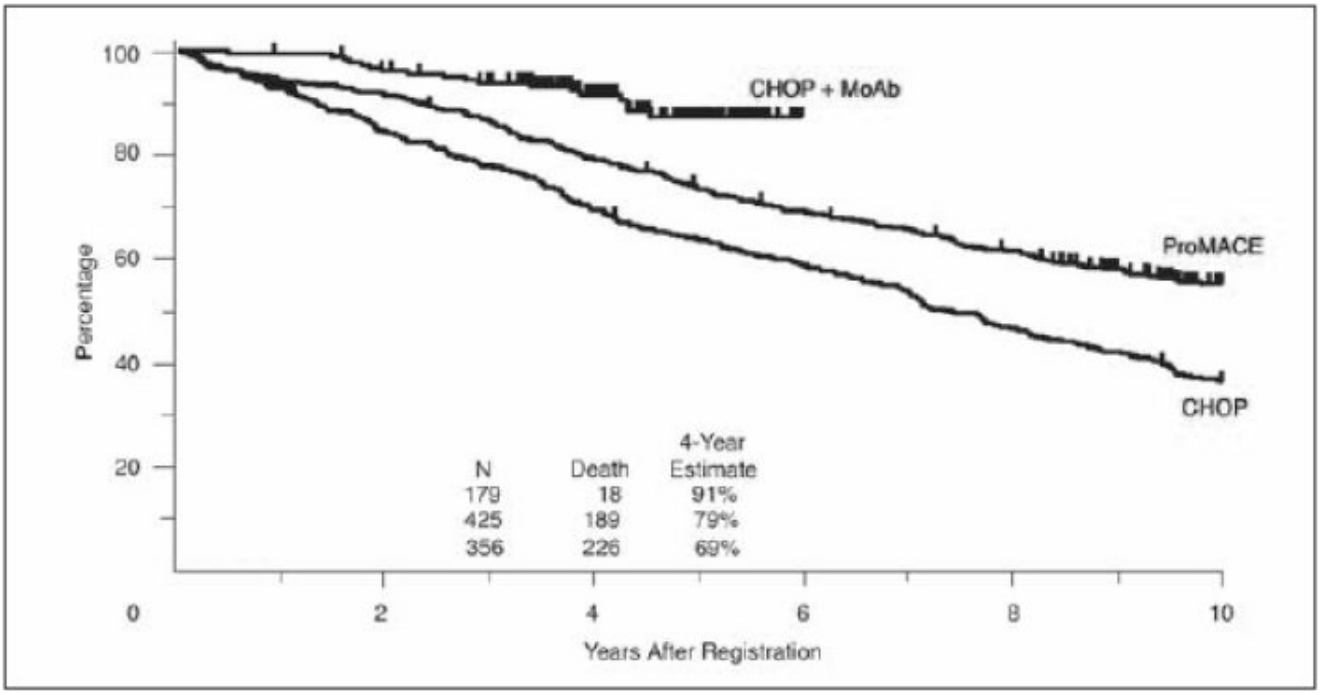

Figure 1.
Overall survival according to chemotherapy regimen: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; MoAb, monoclonal antibody; ProMACE, prednisone, methotrexate, doxorubicin, cyclophosphamide and etoposide. Reprinted with permission.[8]

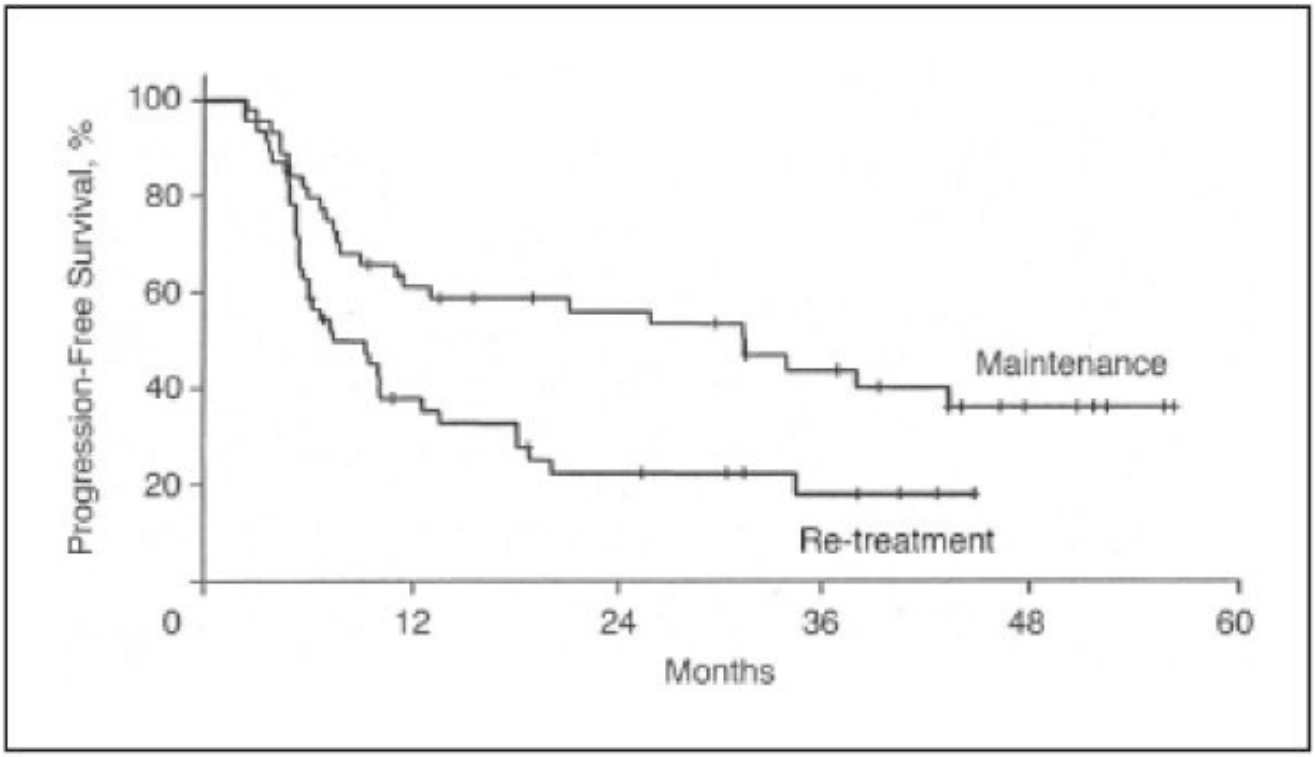

Figure 2.
Progression-free survival in those randomized to maintenance rituximab versus retreatment at time of progression. Reprinted with permission.[22]

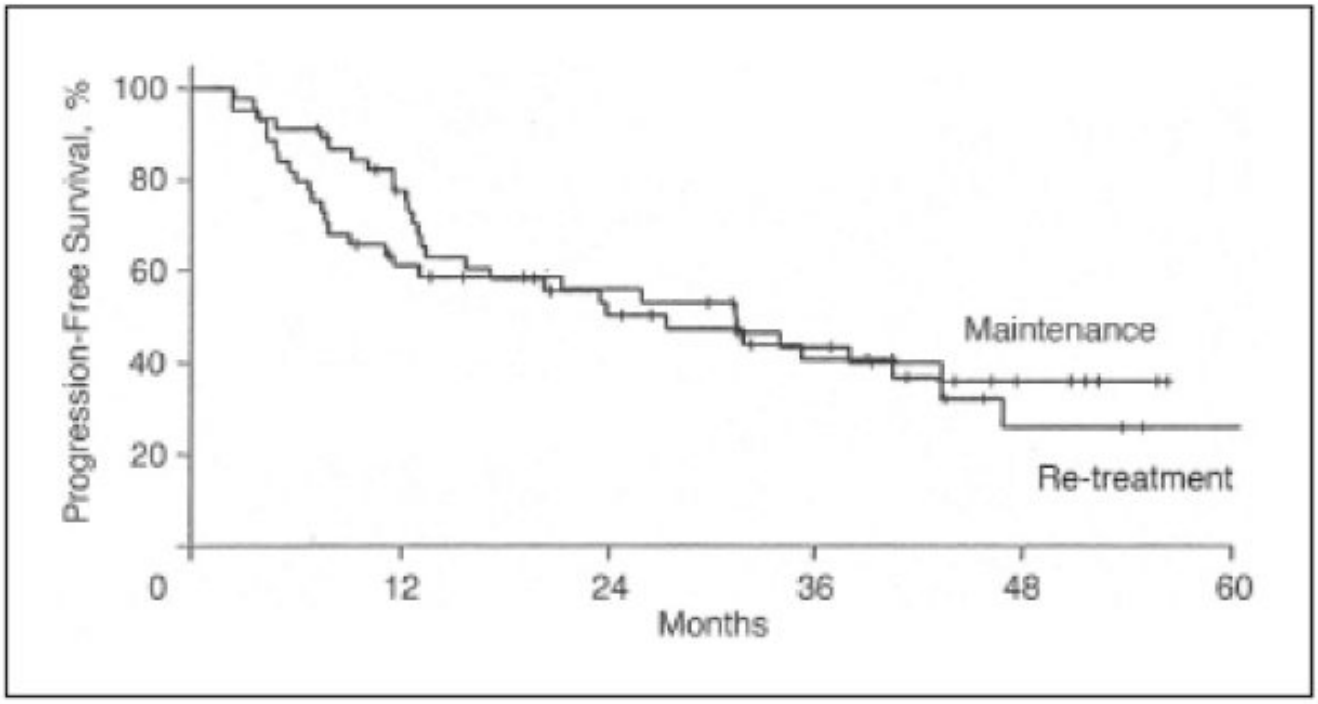

Figure 3.
Duration of response to rituximab treatment according to maintenance or re-treatment at time of progression. Reprinted with permission.[22]

Table 1

Clinical trials of maintenance rituximab

	Number of Patients				
First author, year	**Total**	**Follicular Lymphoma**	**Induction Regimen**	**Rituximab Maintenance Schedule**	**Results**
Hainsworth, 2002 [21]	62	38	R Qwk × 4	Weekly × 4 Q6mo	ORR: 76% PFS: 34 mo
Ghielmini, 2004 [23]	202	202	R Qwk × 4	Q2mo × 4 vs. observation	ORR: 75 vs. 77% EFS: 23.2 vs. 11.8 mo DR: 36 vs. 16 mo
Van Oers, 2006 [43]	474	474	R-CHOP vs. CHOP × 6	Q3mo × 24 mo vs. observation	CR: 29 vs. 16%* PFS: 3.7 vs. 1.3 yrs* 5yr OS: 74 vs. 64%*,&
Hochster, 2009 [45]	164	109	CVP × 6-8	Weekly × 4 Q6mo	PFS: 4.3 vs. 1.3 yrs 3 yr OS: 91 vs. 86%&

ORR, overall response rate; PFS, progression free survival; OS, overall survival; TTF, time to treatment failure; DR, duration of response; EFS, event free survival;

*Long term data;

&Not significant.

Table 2

Clinical trials of rituximab combined with chemotherapy versus chemotherapy alone

	Number of Patients			
First author, year	**Total**	**Follicular Lymphoma**	**Treatment Arms**	**Results**
Forstpointer, 2004 [36]	147	65	R-FCM/FCM	ORR: 94 vs. 70% PFS: NR vs. 21 mo OS: NR for both arms
Marcus, 2005 [6]	321	321	R-CVP/CVP	ORR: 81 vs. 57% TTF: 27 vs. 7 mo DR: 34 vs. 14 mo
Hiddemann, 2005 [29]	428	428	R-CHOP/CHOP	ORR: 96 vs. 90%
Czuczman, 2005 [35]	40	31	RF	ORR: 90% OS: NR TTP: NR
Herold, 2007 [33]	360	360	R-MCP/MCP	ORR: 92 vs. 75% PFS: NR vs. 28.8 mo EFS: NR vs. 26 mo 4yr OS: 87 vs. 74%

R, rituximab; FCM, fludarabine, cyclophosphamide, mitoxantrone; CVP, cyclophosphamide, vincristine, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; F, fludarabine; MCP, mitoxantrone, chlorambucil, prednisolone; ORR, overall response rate; PFS, progression free survival; OS, overall survival; TTF, time to treatment failure; DR, duration of response; EFS, event free survival; NR: not reached.