Maintenance Rituximab is associated with improved clinical outcome in rituximab naïve patients with Waldenstrom Macroglobulinaemia who respond to a rituximab-containing regimen

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Summary

This study examined the outcome of 248 Waldenstrom macroglobulinaemia (WM) rituximab-naïve patients who responded to a rituximab-containing regimen. Eighty-six patients (35%) subsequently received maintenance rituximab (M-Rituximab). No differences in baseline characteristics, and post-induction categorical responses between cohorts were observed. The median rituximab infusions during induction was 6 for both cohorts; and 8 over a 2-year period for patients receiving M-Rituximab. Categorical responses improved in 16/162 (10%) of observed, and 36/86 (41·8%) of M-Rituximab patients respectively, following induction therapy ($P < 0·0001$). Both progression-free (56·3 vs. 28·6 months; $P = 0·0001$) and overall survival (Not reached *versus* 116 months; $P = 0·0095$) were longer in patients who received M-Rituximab. Improved progression-free survival was evident despite previous treatment status, induction with rituximab alone or in combination therapy ($P \leq 0·0001$). Best serum IgM response was lower ($P < 0·0001$), and haematocrit higher ($P = 0·001$) for patients receiving M-Rituximab. Among patients receiving M-Rituximab, an increased number of infectious events were observed, but were mainly ≤grade 2 ($P = 0·008$). The findings of this observational study suggest improved clinical outcomes following M-Rituximab in WM patients who respond to induction with a rituximab-containing regimen. Prospective studies aimed at clarifying the role of M-Rituximab therapy in WM patients are needed to confirm these findings.

Keywords: rituximab, Waldenstrom Macroglobulinaemia, lymphoma, maintenance, CD20.

Rituximab is an active agent in the treatment of Waldenstrom macroglobulinaemia (WM), a CD20-expressing indolent B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of an IgM monoclonal gammopathy (Owen *et al*, 2003). With the use of single agent rituximab, overall response rates of 20–30% have been reported with a standard induction regimen of four weekly infusions, and progression-free survival (PFS) of 1 year (Foran *et al*, 2000; Treon *et al*, 2001; Gertz *et al*, 2004). With the use of an extended schedule of four weekly infusions,

followed by four additional weekly infusions at week 12, response rates of 40–50% and PFS of 16–30 months have been reported (Dimopoulos *et al*, 2002; Treon *et al*, 2005). Because of the non-myelosuppressive nature of rituximab, and its potential to synergize with various anti-neoplastic agents including alkylators, nucleoside analogues, immunomodulatory drugs, and proteasome inhibitors, its investigation in combination regimens has been vigorously pursued (Treon *et al*, 2006; Dimopoulos *et al*, 2009). These studies have generally revealed higher overall response rates (70–90%)

and PFS (3–4 years), and in some studies, improved categorical responses over monotherapy. Despite these successes, most patients with WM eventually show disease progression.

In an effort to improve outcome in WM patients, maintenance rituximab (M-Rituximab) has increasingly become used following reports of improved categorical responses, as well as PFS and/or overall survival (OS) in other indolent B-cell lymphomas (Hainsworth *et al*, 2002, 2009; Ghielmini *et al*, 2004; Forstpointner *et al*, 2006; van Oers *et al*, 2010). However, the efficacy and safety of M-Rituximab has not been investigated in WM patients. As such, we examined the outcome of 248 rituximab-naïve WM patients who responded to a rituximab-based induction therapy, and assessed the impact of M-Rituximab therapy on categorical response attainment, immunoglobulin levels and blood counts, PFS and OS, and safety.

Patients and methods

Study design

We identified all rituximab naïve patients treated at our center with the clinicopathological diagnosis of WM who received a rituximab-containing induction regimen for either untreated or previously treated disease, and who demonstrated at least a minor response to induction therapy. Recommendations for the use of M-Rituximab became routine for all WM patients seen at our centre from May 2001 following the report by Hainsworth *et al* (2001) showing improved clinical outcomes in patients with related indolent B-cell lymphomas. Accordingly, patients received four weekly infusions of rituximab at 375 mg/m^2 every 6 months for M-Rituximab therapy, until December 2004, when, following the report by van Oers *et al* (2004), a more convenient schedule of M-Rituximab was adopted, i.e. one infusion of rituximab at 375 mg/m^2 every 3 months. Despite the routine recommendation for M-Rituximab in all WM patients since 2001, its use was subject to patient tolerance to rituximab during induction, parameters set forth in clinical trials that individual patients elected to participate, and insurance approval. Response determinations were made using modified consensus panel criteria from the Third International Workshop on WM (Kimby *et al*, 2006; Treon *et al*, 2009a,b). A complete response (CR) was defined as having resolution of all symptoms, normalization of serum IgM levels with complete disappearance of IgM paraprotein by immunofixation, and resolution of any adenopathy or splenomegaly. Patients achieving a very good partial response (VGPR), partial response (PR), and a minor response (MR) were defined as achieving a ≥90%, 50–89%, and 25–49% reduction in serum IgM levels, respectively. Progressive disease occurred when serum IgM level increased >25% from the lowest attained response value or progression of clinically significant disease-related symptom(s). PFS and OS were calculated from the start of therapy using the Kaplan–Meier method. Additionally, OS and PFS were compared between

patients on observation *versus* M-Rituximab therapy using the Mantel-Byar method and included time of initiation of M-Rituximab therapy as a time-dependent covariate. The primary endpoints of this study were determination of best categorical response attainment, PFS and OS, and safety among those patients who were observed *versus* those who received M-Rituximab. Changes in immunoglobulin levels and blood counts following M-Rituximab therapy were also assessed for both cohorts. The study was approved by the Dana Farber Cancer Institute/Harvard Cancer Center Institutional Review Board.

Statistical analysis

Comparison of pre- and post-treatment parameters was performed using a two-tailed students *t*-test on Microsoft Excel^{TM} software. For non-parametric testing of pre- and post-treatment responses, Chi-Square test (VassarStats) was used. A *P*-value ≤0·05 was deemed to be significant for the above studies.

Results

Baseline characteristics

Two hundred and forty-eight patients were eligible for study inclusion. Among these patients, 162 (65·3%) and 86 (34·7%) patients underwent either observation or received M-rituximab following induction therapy, respectively. The baseline characteristics for these patients are presented in Table I. No difference in baseline age, serum IgM, IgA, IgG, bone marrow (BM) disease involvement, haematocrit, platelet counts, serum B$_2$M levels, as well as categorical response rates (CR, VGPR, PR and MR) following induction therapy were observed between cohorts. One hundred and eighty-one (73%) patients were previously untreated, with a similar proportion in both cohorts. Prior therapies for the 67 previously treated patients included nucleoside analogues ($n = 40$), chlorambucil ($n = 34$), cyclophosphamide ($n = 7$), bortezomib ($n = 5$), high dose dexamethasone ($n = 4$), thalidomide ($n = 2$), and alemtuzumab ($n = 2$), and did not differ between cohorts. Induction therapy for all patients included rituximab alone ($n = 79$), or in combination with bortezomib ($n = 40$); cyclophosphamide ($n = 44$); immunomodulatory agent ($n = 31$); or a nucleoside analogue-containing regimen ($n = 54$). A similar proportion of patients in both cohorts received induction therapy with rituximab alone and in combination therapy (Table I; $P = 0·265$). Baseline characteristics for patients receiving rituximab alone, and those receiving treatment with rituximab-based combination therapy did not differ between cohorts. The median number of rituximab infusions given as induction was 6 (range 2–12), and was the same for both cohorts ($P = 0·806$), while the median number of rituximab infusions given as maintenance was 8 (range 1–40). M-Rituximab was administered as one infusion

Table I. Characteristics for 248 rituximab naïve patients who underwent either observation or maintenance rituximab therapy following rituximab based induction therapy.

	Patients on observation	Patients who received MR	P-value
N	162	86	NA
Age (years)	61	62	0·755
BM involvement (%)	40	50	0·068
Previously untreated	117 (72·2%)	64 (74·4%)	0·710
Serum IgM (g/l)	36·95	36·4	0·844
Serum IgA (g/l)	0·42	0·49	0·455
Serum IgG (g/l)	4·93	5·53	0·656
Haematocrit (%)	31·0	33·0	0·155
Platelet count ($\times 10^9$/l)	213	162	0·419
Serum β_2M (mg/l)	3·3	2·8	0·626
Induction therapy			
Rituximab alone	56 (34·6%)	23 (26·7%)	0·265
Combination therapy with Rituximab	106 (65·4%)	63 (73·3%)	
Categorical responses Post-induction			
CR	10 (6·2%)	3 (3·5%)	0·611
VGPR	12 (7·4%)	5 (5·8%)	
PR	99 (61·1%)	52 (60·5%)	
MR	39 (24·1%)	24 (27·9%)	

CR, Complete Response; VGPR, Very Good Partial Response; PR, Partial Response; MR, Minor Response.

(at 375 mg/m^2) every 3 months for 63 (73%) patients, and as four weekly infusions (at 375 mg/m^2) every 6 months for 23 (27%) patients, with a median of 24 (range 6–72 months) of treatment. The median follow-up for all patients was 37·9 (range 5·6–127·1 months).

Categorical responses

Categorical responses for those patients immediately following induction therapy appear in Table I, and did not significantly differ for those patients who subsequently were observed or received M-Rituximab. Within the follow-up period, the best categorical responses achieved for those patients observed were as follows: CR ($n = 12$; 7·41%); VGPR ($n = 22$; 13·6%); PR ($n = 90$; 55·6%); MR ($n = 36$; 22·2%), with categorical response upgrade observed in 16/162 (10%) of patients following induction therapy. Among patients who received M-Rituximab during the follow-up period, the best categorical responses achieved were as follows: CR ($n = 14$; 16·3%); VGPR ($n = 11$; 12·8%); PR ($n = 52$; 60·5%); MR ($n = 7$; 8·1%), with categorical response upgrade observed in 36/86 (41·8%) of M-Rituximab patients following induction therapy ($P < 0·0001$).

PFS and OS analysis

Using the Kaplan–Meier method, both PFS (56·3 vs. 28·6 months; $P = 0·0001$) and OS (Not reached versus
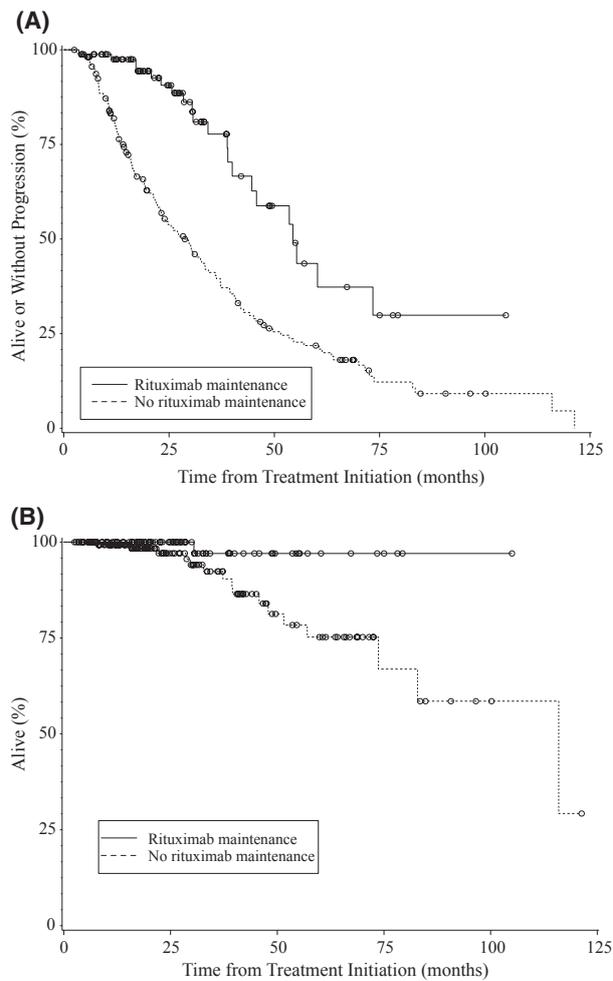

Fig 1. Kaplan-Meier plots for progression-free (A) and overall (B) survival for 248 rituximab-naïve patients who underwent either observation or maintenance rituximab therapy following rituximab-based induction therapy.

116 months; $P = 0·0095$) were longer in those patients who received M-Rituximab when progression or death was calculated from start of treatment (Fig 1). To account for potential zero time shift bias, a Mantel-Byar analysis was also employed and included time of initiation of M-Rituximab therapy as a time-dependent covariate. Both progression (54·4 vs. 28·6 months; $P < 0·0001$) and OS (Not reached versus 116 months; $P = 0·0273$) were longer in those patients who received M-Rituximab. Improved PFS following M-Rituximab therapy was evident despite previous treatment status, induction with rituximab alone or in combination ($P \leq 0·001$). Also, improved PFS following M-Rituximab was observed in patients who received induction therapy with rituximab and a cyclophosphamide-, nucleoside analogue- or bortezomib-containing regimen ($P \leq 0·001$). Among patients receiving M-Rituximab, the median PFS was 53·3 vs. 61·3 months ($P = 0·4931$) for those patients receiving one infusion of rituximab every 3 months compared to those receiving four weekly infusions every 6 months, respectively.

Impact of M-Rituximab therapy on serum immunoglobulins and blood counts

Among patients who underwent observation following induction therapy, the median best serum IgM response was 13·8 (range 0·07–69·7 g/l). In comparison, the best serum IgM response for those patients who received M-Rituximab following induction therapy was 5·98 (range 0·07–41·8 g/l; *P* < 0·0001). We also assessed changes in serum IgA and IgG levels in order to determine the impact of M-Rituximab on 'uninvolved' immunoglobulin levels, by examining the lowest serum IgA and IgG level exhibited by individual patients during the follow-up period. For patients who underwent observation following induction therapy, the lowest median serum IgA level during the follow-up period was 0·33 (range 0·06–16·0 g/l) vs. 0·23 (range 0·06–4·69 g/l) for those patients who received M-Rituximab (*P* = 0·09). Among patients who were observed after induction therapy, the lowest median serum IgG level during the follow-up period was 4·61 (range 0·45–25·9 g/l) vs. 3·51 (range 0·6–11·4 g/l) for those patients who received M-Rituximab (*P* = 0·0008). We also assessed changes in blood counts among patients who were observed and those who received M-Rituximab following induction therapy. Among observation patients, the best haematocrit response achieved during the follow-up period was 38·6% (range 24·9–52·3%), which compared to 40·7% (range 31·7–50·7%) achieved by those patients who received M-Rituximab (*P* = 0·001). No significant difference in platelet count and absolute neutrophil count was observed between these cohorts during the follow-up period.

Adverse events

Adverse events possibly, probably or definitely attributed to rituximab during the entire follow-up period for both cohorts are presented in Table II. Hypersensitivity lead to truncation of planned rituximab therapy in 5 (3·1%) and none (0%) of patients who underwent observation or M-Rituximab therapy, respectively (*P* = 0·248). Among those patients who subsequently received M-Rituximab, hypersensitivity lead to truncation of planned therapy in 4 (4·7%) patients. In another patient, one dose of rituximab was omitted due to reversible neutropenia that was suspected to be rituximab-related. This patient subsequently received two additional infusions of planned M-Rituximab therapy without any incident. During the entire period of follow-up, 33 (20·4%) of the patients who underwent observation after induction therapy experienced at least one infectious event; in comparison, 33 (38·4%) of the patients who underwent M-Rituximab after induction therapy experienced at least one infectious event (*P* = 0·0064). There were 40 infectious events among the 162 observed patients, *versus* 37 infectious events among the 86 patients in the M-Rituximab group. Suspected or documented infections leading to hospitalization occurred in 6 (3·7%) and 3 (3·5%) of the patients who underwent observation or received

Table II. Reported adverse events for 248 rituximab-naïve patients who underwent either observation or maintenance rituximab therapy following rituximab-based induction therapy.

	Patients on observation	Patients who received MR	*P*-value
N	162	86	
Arthralgias	1 (0·6%)	1 (1·2%)	0·773
Bronchitis	11 (6·8%)	8 (9·3%)	0·646
Encephalitis	1 (0·6%)	0 (0%)	0·751
Pneumonia	6 (3·7%)	5 (5·8%)	0·654
Headaches	1 (0·6%)	1 (0·1%)	0·773
Herpes Zoster	2 (1·2%)	3 (3·5%)	0·466
Hypersensitivity	13 (8·0%)	4 (4·7%)	0·462
Neutropenia, with fever	2 (1·2%)	1 (1·2%)	0·577
Neutropenia, without fever	1 (0·6%)	1 (1·2%)	0·773
Sinusitis	12 (7·4%)	13 (15·1%)	0·089
Skin infection	1 (0·6%)	1 (1·2%)	0·773
Syncope	0 (0%)	1 (0·6%)	0·751
Upper respiratory tract infection (NOS)	4 (2·5%)	6 (7·0%)	0·168

MR, M-Rituximab; NOS, not otherwise specified.

M-Rituximab, respectively (*P* = 0·718). Most infectious events during the entire follow-up period in both cohorts involved the respiratory tract. Among patients who underwent observation following induction therapy, 33/40 (83%) of the reported infectious events involved the respiratory tract. All but six of these events were <grade 3. Among patients who received M-Rituximab following induction therapy, 32/37 (87%) of the reported infectious events involved the respiratory tract. All but three of these events were <grade 3; *P* = 0·555 for grade 3 events occurring between cohorts.

Discussion

The paucity of published data on the use of M-Rituximab in WM patients prompted us to investigate the outcome of 248 rituximab-naïve patients who demonstrated a response to a rituximab-based therapy, and who subsequently were observed or who underwent M-Rituximab therapy. The strength of this study is the large population of WM patients included, as well as the long follow-up period available for these patients. In addition, both cohorts exhibited similar baseline and response characteristics following induction therapy, permitting an informative analysis. Despite these strengths, unforeseen biases, which could have influenced patients selected for observation *versus* M-Rituximab therapy, as well as patient follow-up need to be kept in mind when interpreting the outcomes of this retrospective analysis.

While the use of M-Rituximab has not been previously investigated in WM, two previous studies addressed the role of an extended schedule of rituximab administration, i.e. four weekly infusions followed by four more weekly infusions in WM (Dimopoulos *et al*, 2002; Treon *et al*, 2005). These single

arm studies showed higher overall response rates and possibly time to progression in comparison to studies utilizing standard four weekly infusions. However, the impact of long term M-Rituximab in WM has remained to be clarified, largely because of the uncommon nature of the disease as well as priorities by investigators in identifying novel, WM-directed therapeutics.

As part of these efforts, we observed a fourfold improvement in categorical responses in patients receiving M-Rituximab *versus* those who were observed after induction therapy. The achievement of a better categorical response is associated with improved PFS in WM patients treated with a rituximab-containing regimen (Treon *et al*, 2011). However, attainment of CR has been <10% in the majority of WM-directed clinical trials, including most of those incorporating rituximab as induction therapy. It is noteworthy that the CR rate in this study was significantly higher among patients who received M-Rituximab (16·3%), *versus* those who underwent observation (7·4%; $P = 0·05$), a finding that may have contributed to the improvements observed in PFS and OS in this study. Consistent with these findings, patients who underwent M-Rituximab also exhibited significantly better serum IgM responses, as well as improvements in their haematocrit *versus* those patients who underwent observation. These findings and the application of M-Rituximab may be particularly relevant from a clinical benefit point of view for WM patients presenting with morbidity related to serum IgM, i.e. IgM-related neuropathy, cryoglobulinaemia, cold agglutinaemia, and other autoimmune processes, hyperviscosity related to elevations in serum IgM levels, as well as patients presenting with symptomatic anaemia (Treon, 2009).

The important recognition in this study were the significant improvements noted in both PFS and OS in WM patients who received M-Rituximab. Among all patients who received M-Rituximab, PFS was nearly double that of patients who underwent M-Rituximab therapy (56 vs. 28 months). Improved PFS was evident despite previous treatment status, induction with rituximab alone or in combination therapy ($P \leq 0·0001$). OS, defined as death from any cause, was also significantly longer in patients who received M-Rituximab. These observations are consistent with those made in studies addressing the role of M-Rituximab in other indolent B-cell lymphomas (Hainsworth *et al*, 2002, 2009; Ghielmini *et al*, 2004; Forstpointner *et al*, 2006; van Oers *et al*, 2010).

Consistent with the reporting of other studies addressing the role of M-Rituximab in other indolent B-cell lymphomas, we did not encounter any unexpected toxicities with M-Rituximab in WM patients (Hainsworth *et al*, 2002, 2003, 2009; Ghielmini *et al*, 2004; Forstpointner *et al*, 2006; Wenger *et al*, 2008; Taverna *et al*, 2009; van Oers *et al*, 2010). A higher incidence of respiratory tract infections was observed among patients receiving M-Rituximab, though nearly all of these infections were grade 2 or less. In addition, there was no difference in the incidence of hospitalizations over the follow-up period between both cohorts. Respiratory tract infections, particularly bronchitis and sinusitis, are common in WM patients, and have been speculated to be on the basis of IgA and IgG hypogammaglobulinemia, a frequent finding in WM (Treon, 2009; Hunter *et al*, 2010). A recent study found no correlation between serum IgA and IgG levels and recurring infections in WM patients, and recommended against routine intravenous immunoglobulin (IVIG) replacement (Hunter *et al*, 2010). The use of IVIG replacement should however be considered for those WM patients who demonstrate particularly severe recurring sinus and bronchial infections (Treon, 2009). In patients receiving M-Rituximab, and for whom IVIG replacement is being considered, spacing out of these agents should be considered given their potential to compete for similar sets of Fcγ receptors on immune effector cells.

Despite the above findings, many questions remain about the use of M-Rituximab in WM patients. As with other indolent B-cell lymphomas, the ideal schedule and duration of M-Rituximab therapy remains to be determined. Also, these studies did not address the benefit of M-Rituximab over re-treatment upon progression, which is currently being addressed in a prospective study by the Eastern Cooperative Oncology Group, utilizing rituximab in other indolent B-cell lymphomas (Kahl *et al*, 2007).

In summary, the findings of this observational study suggest improved clinical outcomes following M-Rituximab in WM patients who respond to induction with a rituximab-containing regimen. Prospective studies aimed at clarifying the role, ideal administrative schedule and duration for M-Rituximab therapy in WM patients are needed to confirm these findings.

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