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Original article

Extended rituximab therapy in Waldenström's macroglobulinemia

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On behalf the Waldenström's Macroglobulinemia Clinical Trials Group

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Background: Waldenström's macroglobulinemia (WM) is a CD20 expressing B-cell malignancy represented by the pathological diagnosis of IgM secreting lymphoplasmacytic lymphoma. Major response rates of 30% have been reported in most studies with standard dose rituximab, i.e. 4 weekly infusions at 375 mg/m^2/week.

Methods: In an effort to increase rituximab activity in WM, an extended dose schedule employing two sets of four (375 mg/m^2/week) infusions at weeks 1–4 and 12–16 was evaluated. Expression of the complement resistance antigens CD46, CD55 and CD59 was also evaluated on tumor cells pre- and post-therapy to determine impact on response.

Results: Twenty-nine patients were enrolled and 26 patients completed the intended therapy. On an intent to treat analysis, 14 (48.3%) patients achieved a partial response, and 5 (17.2%) patients achieved a minor response. Responses were observed in 18/24 (75%) patients with a serum IgM level of <6000 mg/dl, and only 1 of 5 (20%) patients with a level of >6000 mg/dl ($P = 0.03$). The median time to best response was 17 months, and only 2 of 19 responding patients progressed with a median follow-up of 29 months. No differences in baseline expression of the complement resistance antigens CD46, CD55 and CD59 were observed among responding and non-responding patients, although post-therapy CD55 expression was higher in non-responding patients ($P = 0.002$).

Conclusions: These data show that extended rituximab therapy is active and may lead to more major responses over standard dose rituximab in WM. WM patients with serum IgM levels of <6000 mg/dl are more likely to benefit from extended rituximab therapy.

Key words: Waldenström's macroglobulinemia, lymphoplasmacytic lymphoma, rituximab, CD46, CD55, CD59

Introduction

Waldenström's macroglobulinemia (WM) is a distinct B-cell lymphoproliferative disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of an IgM monoclonal gammopathy [1]. This condition is considered to be lymphoplasmacytic lymphoma as defined by the REAL and WHO classification systems [2, 3].

The treatment options for patients with WM have tended to employ therapies used in either multiple myeloma (MM), chronic lymphocytic leukemia (CLL) or non-Hodgkin's lymphoma (NHL). Oral alkylator drugs such as chlorambucil, as well as the nucleoside analogue drugs cladribine and fludarabine, are in common use [4]. More recently, monoclonal antibodies have successfully been used to treat WM patients. Most of these efforts to date have centered on the use of rituximab, a chimeric monoclonal antibody which targets CD20, an antigen that is widely expressed on tumor cells in WM [5]. The successful use of rituximab in WM was noted by us in a patient who showed a marked reversal in his anemia and had a response that lasted over 19 months following treatment with standard rituximab therapy (i.e. 4 weekly infusions at 375 mg/m^2/week) [6]. Using standard rituximab therapy, Byrd et al. [7] subsequently demonstrated partial responses (defined as a ≥50% decrease in serum IgM) in 4 of 7 (57%) heavily pretreated WM patients with a median progression-free

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survival of 6.6+ months. In a larger experience of single-agent rituximab use in WM, we reported on the outcome of 30 WM patients who had a median of one prior therapy and received treatment with rituximab (median 4; range 1–11.3 weekly infusions) [8]. Eight (27%) patients achieved a partial response following treatment with rituximab in this study. The time to treatment failure (TTF) for responding patients was 8.9 months (3–20+ months). Interestingly, 63% and 50% patients had an increase in their hematocrit and platelet counts, respectively, which included many patients who attained a minor response or had stable disease. Importantly, 23.3% of these patients were either transfusion or erythropoietin dependent before therapy, whereas only 3.3% of these patients required such support after rituximab. Other experiences with standard dose rituximab have been reported in WM with comparable response rates including a recent study by the Eastern Cooperative Oncology Group (ECOG) in which 35% of untreated patients, and 20% of previously treated patients achieved a partial response [9–11].

In an effort to increase the clinical activity of rituximab therapy, we and others have examined the use of an extended schedule of rituximab administration utilizing an extended schedule that was previously evaluated by us in patients with multiple myeloma [12], in which eight infusions of rituximab were administered at 375 mg/m^2/week at weeks 1–4 and 12–16. Using this schedule, Dimopoulos et al. [13] reported partial responses in 44% of WM patients and with a median follow-up of 16 months, the median time to progression was not reached. In this manuscript, we report our experiences with extended rituximab therapy in WM patients who have been observed for a median follow-up period of 29 months. As part of these studies, we also addressed the role of the complement resistance antigens, CD46, CD55 and CD59, as potential modulators of rituximab clinical activity in WM since in previous work by us and others, expression of the complement resistance antigens CD55 and CD59 were associated with *in vitro* resistance to rituximab mediated complement lysis of B-cell tumor cells [14–16]. Blockage, cleavage or down-regulation of these antigens led to enhanced complement lysis of B-tumor cells by rituximab [14–18]. As such, the expression of the complement resistance antigens CD46, CD55 and CD59 on BM lymphoplasmacytic cells was evaluated before, and following extended rituximab therapy and correlated to its clinical activity.

Patients and methods

Study design and treatment

Patients with a clinicopathological diagnosis of WM using consensus panel criteria [1] with tumor cells expressive of CD20 as determined by flow cytometric analysis or immunohistochemistry, who did not have more than two prior therapies, and who were symptomatic and in need of therapy were eligible for this clinical trial. All patients provided informed written consent and the protocol was approved by the institutional review boards at all of the participating enrollment centers. The intended therapy consisted of four weekly infusions of rituximab at 375 mg/m^2/weekly. Patients that were tolerating therapy and did not demonstrate evidence of progressive disease received a second 4-week course of rituximab at week 12. Twenty-nine patients were enrolled in this clinical trial which constituted a nonrandomized phase II study, and utilized a Simon two-stage design in which the sample size determination was based on response rate. Sample size calculation was based on the assumption that the expected response rate would be at least 35%. Therefore, to have a 95% confidence interval (CI) of approximately ±20%, a sample size of 27 was required. In the first stage, 13 eligible patients were enrolled with second cohort enrollment to continue if four or more patients responded to therapy. Sixteen more eligible patients were entered the study, once four responses among the initial cohort were observed. Differences in the response rate between patient groups were evaluated for significance using a two-tailed Fisher's exact test (VassarStats). A P value ≤ 0.05 was deemed to be significant.

Response determination

A baseline evaluation was obtained within 28 days before initiation of the first course of rituximab therapy and consisted of patient history, physical examination and laboratory studies including determination of serum IgM levels by nephelometry, a complete blood count and differential, and BM biopsy and aspiration. Patients underwent restaging studies 11 weeks following the first course of rituximab therapy. As part of their response evaluation, all patients underwent history and physical examination, laboratory studies consisting of a complete blood count and differential, serum IgM levels, and bone marrow biopsy and aspiration.

Response determinations were made on an intent to treat basis. A complete response 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 partial response and a minor response were defined as achieving a ≥50% and ≥25% reduction in serum IgM levels, respectively [8]. Patients with stable disease were defined as having ≤25% change in serum IgM levels, in the absence of new or increasing adenopathy or splenomegaly and/or other progressive signs or symptoms of WM. Progressive disease was defined as occurring when a greater than 25% increase in serum IgM level occurred from the lowest attained response value or progression of clinically significant disease related symptom(s) [8]. Time to disease progression (TtP) was calculated from the start of rituximab therapy using the Kaplan–Meier method, and differences in the curves were tested for statistical significance using the log rank test [9].

Antibodies and immunophenotypic analysis of cells

BM aspirates were washed three times in phosphate buffered saline (PBS) and resuspended to their original volume in 1% bovine serum albumin (Sigma Chemical Co., St Louis, MO) in PBS. One hundred microliters (μl) of patient cell suspension was then aliquotted to tubes and stained with the following directly conjugated antibodies: CD20 PERCP, CD19 APC, KAPPA/LAMBDA SIMULSET (Becton Dickinson, San Jose, CA); CD55 FITC (Serotec); CD46 FITC and CD59 FITC (Beckman Coulter, Fullerton, CA, Immunotech, Fullerton, CA). Cells were incubated at room temperature for 15 min, followed by red cell lysis using Becton Dickinson's (BD) lysis buffer. Mononuclear cells were then incubated for 10 min followed by centrifugation (5 min at 200 *g*). The supernatant was discarded and the cell pellet was then resuspended in PBS for a final centrifugation as before. The resulting cell pellet was resuspended in 0.5 ml of 1% paraformaldehyde/PBS and analyzed by flow cytometric analysis within 2 h of staining using a FACS Calibur equipped with a 488 nm argon and a diode laser. The instrument was calibrated according to the manufacturer's instructions using BD CaliBrite beads. Forward and side scatter settings, as well as compensation settings, were optimized using singly stained

Table 1. Summary of pre-therapy clinical and laboratory features for all patients enrolled on study

Median age	65 (43–90)
Median prior therapies	1 (0–2)
No prior therapy	12 (41%)
Median BM involvement	25 (5–90%)
Adenopathy and/or splenomegaly	5 (17%)
IgM ≥3000 mg/dl	19 (66%)
Hct <30%	10 (35%)
PLT <100 000/mm^3	8 (28%)

BM, bone marrow; Hct, hematocrit; PLT, Platelet count.

lymphocytes. Twenty thousand cells were acquired for each sample analyzed. Comparison of pre- and post-rituximab parameters was carried out using a two-tailed Student's *t*-test on Microsoft Excel™ software. A *P* value ≤0.05 was deemed to be significant.

Results

Patients and disease characteristics

The clinical features of the 29 WM patients enrolled in this study are summarized in Table 1. The median age of these patients was 65 (range 43–90) years old. Median number of treatments before rituximab therapy was 1 (range 0–2 prior therapies). Twelve (41%) patients had no prior therapy. Of the 17 previously treated patients, 11 and 3 patients progressed or showed stable disease to their previous therapy, respectively whilst 3 patients relapsed off their preceding therapy. Median pre-therapy BM involvement with lymphoplasmacytic cells was 25% (range 5%–90%), and median serum IgM level was 3560 mg/dl (range 1990–9240 mg/dl). Nineteen (66%) patients had an IgM level of >3000 mg/dl. Median pre-therapy hematocrit and platelet count for all enrolled study patients was 31.6% (range 21.7%–43.9%), and 185 000/μl, respectively. Ten (35%) and 8 (28%) of the patients had a hematocrit ≤30% and a platelet count of ≤100 000/mm^3, respectively.

Of the 29 patients enrolled in the study, 28 completed their first course of therapy. One patient with progressing disease received only two of the four prescribed infusions and was taken off the study. Two patients were taken off the study after receiving only one course (four infusions) of rituximab. One of these patient, who previously had been treated with fludarabine and steroids died of *Pneumocystis carinii* pneumonia, an event deemed by the drug and safety monitoring board overseeing this trial to be unrelated to protocol therapy. The second patient developed monoarticular arthropathy attributed to rituximab following the first course of therapy and was treated with steroids. Therefore, 26 patients completed both courses of the intended rituximab therapy.

Response

The individual changes in serum IgM levels at best response for all patients are shown in Figure 1. Median IgM levels for all 29 patients declined from 3560 mg/dl (range 1990–9240 mg/dl) pre-therapy to 1840 mg/dl (range 174–10 300 mg/dl) at best response ($P = 0.02$). Pre-therapy, 19/29 (65.5%) patients demonstrated an IgM level ≥3000 mg/dl; following treatment, only 8 of 29 (27.5%) had an IgM level ≥3000 mg/dl. Overall, 19 of the 29 (65.5%) patients enrolled in this study demonstrated at least a minor response as their best response. Of these patients, 14 (48.3%) achieved a partial response, and 5 (17.2%) achieved a minor response. No complete remissions were observed. In addition, 3 (10.3%) patients had stable disease following treatment with rituximab. Four patients (13.8%) had clear progression of their disease despite rituximab therapy and were deemed to be non-responders. Among partial responders, the median time for a 50% reduction in serum IgM was 7 (range 3–19) months. Of particular interest was the observation that pre-therapy IgM levels served as a determinant of response (Figure 2). Eighteen of 24 (75%) patients who had a serum IgM level of <6000 mg/dl responded, whereas only 1 of 5 (20%) patients with an IgM level of >6000 demonstrated a response, which was a MR ($P = 0.03$). In contrast, pre-therapy BM involvement did not serve as an independent determinant for rituximab response (data not shown). The median time to best response for responding patients was 17 (range 3–32) months, and was not significantly different among those patients who achieved a partial response (16.6 months) and a minor response (21.5 months) ($P = 0.78$).

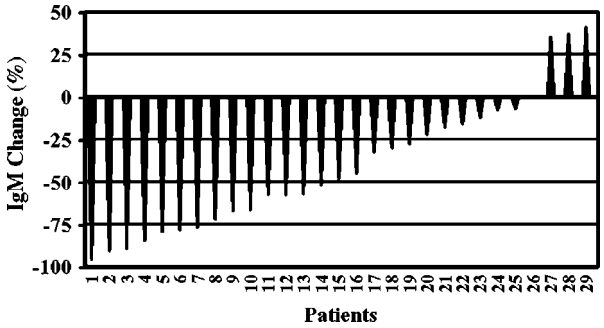

Figure 1. Individual changes (%) in serum IgM levels following treatment with extended rituximab.

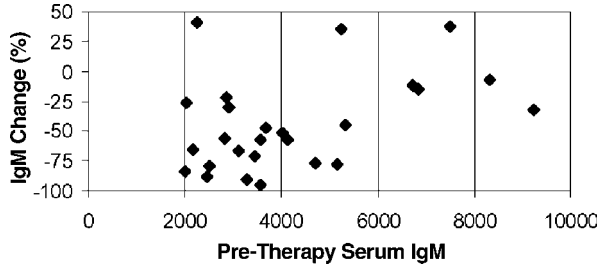

Figure 2. Individual pre-therapy IgM levels as a determinant of response following therapy.

Time to progression

The median time to progression for all patients was 14 months, and was similar for untreated (17 months) and previously treated (14 months) patients ($P = 0.363$). With a median follow-up of 29 (range 12–36+) months, only 2 of

the 19 responding patients have progressed. Response duration for patients with a partial response and a minor response was 18+ and 20+ months, respectively, and was not significantly different ($P = 0.84$). All three patients with stable disease progressed at 9, 24 and 29 months.

Changes in hematological parameters in WM patients treated with rituximab

Before therapy, 11 (37.9%), and 8 (27.5%) of the 29 patients demonstrated a hematocrit of ≤30% and a platelet count of ≤100 000/μl, respectively. Following therapy, at best response, 4 (15.4%) and 1 (3.8%) of the 29 patients demonstrated a hematocrit of ≤30% and a platelet count of ≤100 000/μl, respectively. A significant increase in the median hematocrit was noted for all patients from 31.6% (range 24.1%–43.9%) before therapy to 38.3% (range 26%–45.2%) following rituximab therapy ($P = 0.01$), with 15 of the 29 (52%) patients demonstrating a hematocrit rise of >2%. Before therapy, five patients required erythropoietin. Following therapy, 3 responding patients (2 partial and 1 minor) no longer required erythropoietin, whereas 2 non-responders continued to require such support. The median platelet count also increased following rituximab therapy from 185 000/μl (range 44 000–492 000/μl) to 201 000/μl (range 90 000–426 000/μl), although this increase was not statistically significant ($P = 0.5$).

Toxic effects

Overall, treatment was well tolerated with most toxic effects attributed to rituximab rated as grade 1 or 2 using National Cancer Institute Common Toxicity Criteria version 2. Most of these toxic effects were infusion related, and typically occurred with the first infusion. Two patients experienced grade 3 toxicity attributed to rituximab. One patient experienced a grade 3 monoarticular arthralgia after receiving four infusions of rituximab which resolved after a 2-week course of steroid therapy. Another patient experienced reversible grade 3 neutropenia during the first course of rituximab therapy. One patient previously treated with fludarabine and steroids died of *Pneumocystis carinii* infection while on study. The circumstances of this patient's death were reviewed by the Drug and Safety Monitoring Board (DSMB) who deemed this event to be unrelated to protocol therapy.

Complement resistance antigen expression

As part of these studies, we also evaluated whether expression of complement resistance antigens by tumor cells affected the clinical activity of rituximab in WM patients. Expression of the complement resistance antigens CD46, CD55 and CD59 was determined on BM lymphoplasmacytic cells ($CD19^+$, light chain restricted) before therapy, and at 3 and 6 months following initiation of therapy for 18 (14 responding, 3 stable disease, 1 non-responding) patients. These studies demonstrated that CD46, CD55 and CD59 were widely expressed on BM lymphoplasmacytic cells at baseline. Eighteen of 18 (100%), 17/18 (94.4%), and 17/18 (94.4%) of patients expressed CD46, CD55 and CD59, respectively, with antigen expression on ≥90% of BM lymphoplasmacytic cells and mean fluorescence intensities (MFI) as follows: CD46 (100%; MFI 60.37, range 52.4–111.6); CD55 (88.9%; MFI 51.47, range 16.24–1208.24); CD59 (77.8%; MFI 31.27, range 14.43–91.67). Comparison of pre-therapy expression for CD46, CD55 and CD59 between all responders and those patients with stable disease or no response demonstrated no significant difference (data not shown).

We next undertook an analysis of changes in the MFI of CD46, CD55 and CD59 on lymphoplasmacytic cells following rituximab therapy for 11 (7 responding, 3 stable disease, 1 non-responding) patients for whom follow-up data were available. Comparison of the baseline MFI for CD46, CD55 and CD59 to those obtained following rituximab therapy at 3 and 6 months among responding patients showed no significant differences, although there was a trend for CD55 expression to decrease (Figure 3A). Similar to responding patients, no significant change in the MFI of CD59 on persisting lymphoplasmacytic cells was seen following rituximab therapy at 3 and 6 months among stable disease and non-responding patients (Figure 3B). Insufficient data prevented a meaningful comparison for CD46 MFI changes to be determined in stable disease and non-responding patients. In contrast to the decreased expression of CD55 observed on residual lymphoplasmacytic cells among responding patients, a significant increase in CD55 expression was observed on persisting tumor cells in stable disease and non-responding patients following rituximab therapy at 6 months ($P = 0.006$) (Figure 3B).

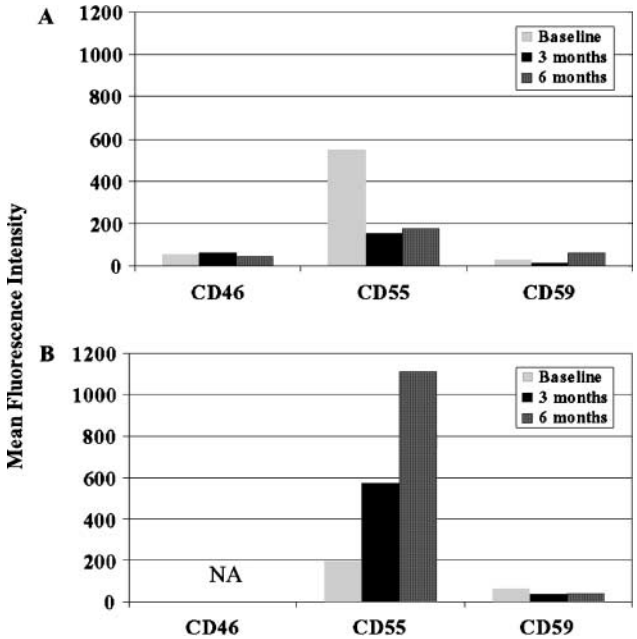

Figure 3. Changes in MFI of complement resistance antigens on bone marrow lymphoplasmacytic cells following extended rituximab therapy in responding patients ($N = 7$) (**A**) and non-responding patients ($N = 4$) (**B**). $P^1 = 0.006$ for comparison of CD55 levels at baseline versus at 6 months on persistent tumor in non-responding patients' cells; $P^2 = 0.002$ for comparison of CD55 levels at 6 months between responding and non-responding patients.

Comparison of the baseline MFI for CD55 revealed no significant differences between responders, and stable disease and non-responding patients in this subset analysis ($P = 0.1$). However, a significant difference in the MFI of CD55 was seen following rituximab therapy at 6 months between these two groups ($P = 0.002$).

Discussion

In an effort to increase the clinical benefit of rituximab in WM, we examined the use of an extended dose schedule which employed eight infusions of rituximab delivered at 375 mg/m^2/week at weeks 1–4 and 12–16. A partial response was observed in 48.3% and a minor response in 17.2% of the patients enrolled in this study. Moreover, with a median follow-up of 29 months, only 2 of the 19 responding patients demonstrated progressive disease. Similar results were obtained with an identical dose schedule by Dimopoulos et al. [13], in whose study 44% and 12% of patients achieved partial and minor responses, respectively. The median time to progression in this study was also not reached with a shorter median follow-up of 16 months. By comparison, partial responses were observed in 20%–30% of patients in most studies examining standard dose rituximab in WM (Table 2). The impact of extended rituximab therapy on prolonging response durations over standard dose rituximab remains to be clarified. Response durations of 16+ to 29+ months were observed in the study by Dimopoulos et al. [13] and in this study, respectively. In comparison, response durations of 27+ months have recently been reported in an ECOG study examining standard dose rituximab in WM patients, although other standard dose rituximab studies reported response durations of about 8–9 months (Table 2).

An intriguing finding in this study was the late response activity, as evidenced by the median time to best response of 17 (range 3–32) months. Continued declines in serum IgM beyond 1 year were also noted among some patients in the study by Dimopoulos et al. [13]. One possibility for this finding is that rituximab may differentially target members of the malignant clone in WM. It is well recognized that in WM, the malignant clone encompasses mature B cells, lymphoplasmacytic cells and plasma cells [2]. Initial elimination of precursor mature B cells and lymphoplasmacytic cells by rituximab, might then lead to eventual clonal extinction of IgM producing plasma cells, which may be less susceptible to rituximab, possibly on the basis of either dim or absent expression of CD20 [6, 12, 19] or expression of serotherapy protective antigens [15, 20].

Table 2. Studies with standard and extended rituximab dose in WM, including this study by the Waldenstrom's Macroglobulinemia Clinical Trials Group (WMCTG)

	N	Median no. of infusions	Major RR	Response duration
Byrd et al. [7]	6	4	57%	6.6+ months
Treon et al. [8]	30	4	27%	8.4 months
Weber et al. [9]	8	4	75%	9.0 months
Foran et al. [10]	7	4	29%	NA
Gertz et al. [11]	69	4	27%	27+ months
Dimopoulos et al. [13]	27	8	44%	16+ months
WMCTG	29	8	48%	29+ months

Major response rate (RR) reflects percentage of patients achieving partial and complete responses only.

As in our previous studies employing four infusions of rituximab in WM [8], improvements in hematological function were again observed. Before therapy, anemia (hematocrit ≤30%) and thrombocytopenia (platelets ≤100 000/mm^3) were observed in 37.9% and 27.5% of patients, respectively. After rituximab therapy anemia and thrombocytopenia were observed in only 17.2% and 3.8% of patients.

The level of circulating IgM may predict those patients who are more likely to benefit from rituximab therapy. Dimopoulos et al. [13] in their study of extended rituximab therapy in WM patients, observed a response rate of 58% for those patients who had a serum IgM level of <4000 mg/dl versus 13% in those with a serum IgM level of >4000 mg/dl. Similarly, we observed an overall (complete plus partial) response rate of 75% for patients who had a serum IgM level of <6000 mg/dl, whereas only 20% of patients with a serum IgM level of >6000 mg/dl demonstrated a response. Importantly, no correlation between bone marrow involvement and response to rituximab was observed, and patients with a serum IgM level of >6000 and <6000 mg/dl both had one median prior therapy signifying that the number of prior therapies did not serve as a determinant of response. The mechanism, therefore, for this finding remains to be clarified, and it remains possible that the differentiation state of the tumor may be important (i.e. that rituximab is less effective on more differentiated, highly IgM secreting plasma cells) or that circulating IgM *per se* may affect a response to rituximab.

The combination of rituximab therapy in conjunction with chemotherapy has also been explored. Weber et al. [21] examined the combination of cladribine and cytoxan in combination with rituximab in 17 patients with newly diagnosed WM. A reduction of greater than 75% in serum IgM levels, which defined a partial response, was observed in 94% of patients who received combination therapy with cladribine, cytoxan and rituximab. Whereas the response rate appeared to be on a par with the outcomes of historical controls who had received treatment with cladribine alone (93%), and cladribine plus cytoxan (92%), median response durations appeared to have been greatly extended with the addition of cytoxan and rituxan to cladribine therapy. In an ongoing study, the Waldenstrom's Macroglobulinemia Clinical Trials Group is examining the combination of rituximab and fludarabine. Patients in this study are receiving six cycles of fludarabine along with eight infusions of rituximab over 31 weeks. At least a 25% reduction in serum IgM levels was observed in 91% of patients, and only 3 of 39 responders progressed with a median follow-up of 17 months.

While therapy with rituximab has been well tolerated in the above series, abrupt increases in serum IgM levels have been commonly observed in WM patients following treatment with rituximab, including in one patient who had a subdural hemorrhage after her serum viscosity level tripled following rituximab therapy [23]. The cause for this finding remains to be defined, and close monitoring of serum IgM and viscosity levels appears warranted while patients are receiving therapy with rituximab.

As part of these studies, we also evaluated whether tumor cell expression of complement resistance antigens CD46, CD55 and CD59 affected the clinical activity of rituximab in WM patients. CD46, CD55 and CD59 were found to be widely expressed on BM lymphoplasmacytic cells, and no correlation with their presence and level of expression with clinical response to rituximab was observed. A lack of correlation with pretreatment tumor cell expression of CD46, CD55 and/or CD59 and rituximab response has also been reported in studies involving patients with other B-cell malignancies [24, 25]. Of particular interest though in this study was the unexpected observation that CD55 expression significantly increased on persistent BM lymphoplasmacytic cells in non-responding patients, whereas it declined on residual tumor cells among responders. A similar observation was made by Bannerji et al. [25] who recently reported increased expression of CD55 and CD59 on persistent chronic lymphocytic leukemia (CLL) cells in non-responding patients following rituximab therapy, although significance was only achieved for the latter antigen. Clonal selection of tumor cells with increased levels of expression for CD55 and/or CD59 would have been predicted for responding, instead of non-responding patients to rituximab therapy, if indeed significant complement mediated killing of tumor cells was occurring. The mechanism for this finding remains to be discerned, although it may involve a paradoxical induction of these complement resistance antigens by rituximab. Since CD55 may also play a role in blocking effector cell killing, the finding of higher levels of expression for this antigen on rituximab-resistant BM lymphoplasmacytic cells in this study may also explain a lack of tumor cell killing on the basis of antibody directed cell cytotoxicity (ADCC) [26]. Strategies directed at selectively inhibiting the expression and/or function of complement resistance antigens on malignant B cells might, therefore, be expected to produce improvements in clinical responses in patients receiving rituximab.

In conclusion, extended rituximab therapy is highly active and produces prolonged responses in patients with WM. WM patients with serum IgM levels of <6000 mg/dl are more likely to benefit from extended rituximab therapy.

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