Symposium article

Treatment of mantle-cell lymphoma with Rituximab (chimeric monoclonal anti-CD20 antibody): Analysis of factors associated with response

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Summary

Background: A retrospective analysis was performed to delineate the factors associated with response, and to determine the duration of response, in 87 patients with CD20-positive mantle-cell lymphoma (MCL) treated with Rituximab (chimeric monoclonal anti-CD20 antibody) in two prior studies.

Patients and methods: Patients with newly-diagnosed MCL (MCL1, $n = 37$), and previously-treated MCL (MCL2, $n = 50$), received single-agent Rituximab, in the context of two multicentre clinical studies using different schedules and doses, conducted in 1996 and 1997. A follow-up analysis was performed at the end of 1998, including all 81 patients who completed therapy. Statistical modeling of factors associated with response was performed using ordered logistic regression. The duration of complete (CR) and partial response (PR), and the time to disease progression (TTP), were also derived.

Results: The overall response rate (RR) was 34% (30 of 87) (81 evaluable patients, RR 37%; CR 14%), and was equivalent for MCL1 and MCL2. On univariate analysis, elevated LDH ($P = 0.004$); prior therapy with alkylating agents ($P = 0.01$) or fludarabine phosphate ($P = 0.04$); WHO performance status = 2 ($P = 0.02$); MCL2 refractory to last prior therapy ($P = 0.04$); and splenomegaly ($P = 0.04$), each at the time of treatment with Rituximab, were significantly associated with a lower RR. On multivariate analysis, only LDH ($P = 0.007$) and prior alkylating agents ($P = 0.03$) retained statistical significance.

At a median follow-up of 1.4 years, the median TTP was 7 months. The median duration of response was one year, and was significantly longer for patients achieving CR vs. PR ($P = 0.04$).

Conclusions: Rituximab is active in MCL, and can induce complete responses in a minority of patients. Elevated LDH at the time of therapy, and prior therapy with alkylating agents, are associated with a significantly lower RR. The duration of response of one year is similar to that previously reported in follicular lymphoma.

Key words: anti-CD20, chimeric monoclonal antibody, mantle-cell lymphoma, R.E.A.L. Classification, Rituximab

Introduction

Mantle-cell lymphoma (MCL) is an uncommon sub-type of B-cell non-Hodgkin's lymphoma (NHL), representing approximately 6% of new cases [1]. Although frequently responsive to cytotoxic chemotherapy, complete remission is uncommon, and disease progression is the rule [2–4]. The clinical course of MCL is characterised by a short median survival (approximately three years), and very few long-term survivors [1–4]. MCL is therefore considered incurable with present therapy.

Rituximab, a chimeric monoclonal anti-CD20 antibody [5], has been evaluated primarily in previously-treated follicular lymphoma, where it has demonstrated significant activity [6, 7]. The median duration of response has been reported to be approximately one year [7]. However, until recently, little was known about the efficacy of Rituximab in MCL, which also expresses CD20, or in patients with newly-diagnosed disease.

In two recent studies, significant activity of Rituximab was noted in patients with MCL, both newly-diagnosed and previously-treated [8, 9]. In order to further characterise its activity, a retrospective analysis including both sets of patients was performed in December 1998, to delineate the factors associated with response to Rituximab, and with the duration of response. The results form the basis of this report.

Patients and methods

Patients

Eighty-seven patients with MCL received single agent Rituximab in two multicentre studies evaluating its efficacy in patients with: (i) 'intermediate-grade' NHL [8] (according to the NCI Working Formulation) [10]; and (ii) MCL, immunocytoma, and small B-lymphocytic lymphoma [9] (Kiel Classification) [11]. The study protocols were approved by the local hospital ethics committee for each participating

centre, and informed written consent was obtained from each patient prior to therapy. All patients were treated between December 1996, and December 1997. The participating centres and principle investigators are noted in the Appendix.

Six patients did not complete therapy, and were inevaluable for response, the primary outcome of this analysis. They were therefore not included in the analysis of response, response duration, and time to progression, but have been included in the analysis of overall survival from treatment. The reasons for not completing therapy were: Death due to splenic rupture following the first infusion of Rituximab (n = 1); anaphylaxis (n = 2); atrial fibrillation and congestive cardiac failure (n = 1); and, abnormal liver function tests (n = 1). The remaining patient withdrew consent to continue with treatment prior to its completion.

The diagnosis of MCL was assigned at the individual centre according to the criteria of the proposed R.E.A.L. Classification [12]; tumour cell expression of CD20 was confirmed in all cases. Both newly-diagnosed (MCL1) and previously-treated (MCL2) patients were eligible; those with central nervous system involvement, World Health Organisation (WHO) performance status (PS) >2, or active hepatitis B or C, or HIV infection, were excluded. The characteristics of the 87 patients at the time of treatment are noted in Table 1.

Table 1. Baseline clinical characteristics (n = 87).

Characteristics	n
Age (in years)	
Median	62
Range	33–83
Sex	
Male	66
Female	21
WHO performance status	
0	41
1	33
2	13
Extent of disease (data available on n =81)	
Limited	5
Extensive	76
Rituximab dose and schedule	
375 mg/m^2/week × 4	74
375 mg/m^2/week × 8	4
500 mg/m^2/week × 8	9
Disease status at treatment (data available on n = 86)	
Newly-diagnosed	37
Relapsed	24
Refractory	22
'Consolidation of prior response'	3
No of previous treatments (n = 50)	
Median	2
Range	1–9

Treatment

Rituximab was administered as a single agent by intravenous infusion over several hours once weekly for either four or eight weeks, in accordance with guidelines issued by Roche Pharmaceuticals (Basel, Switzerland). The majority of patients received a four-week course of therapy (375 mg/m^2 × 4, n = 74), although 13 received an eight-week course. The latter 13 patients were randomised to receive either 375 mg/m^2 (n = 4) or 500 mg/m^2 (n = 9) [15]. Patients received an anti-pyrexic and an anti-histamine as prophylaxis prior to therapy, although concomitant administration of corticosteroids was not permitted in either study. Restaging studies (CT scanning and bone marrow trephine biopsy) were performed one and two months following the completion of therapy.

Response and follow-up

Further information on all patients was obtained from the individual investigators in December 1998, including details of the clinical and biological characteristics of the MCL at the time of treatment with Rituximab, and follow-up data. Follow-up data included the dates of further treatment and disease progression, and of last follow-up or death. The details of previous treatments, and dates of therapy and response to Rituximab, were obtained from the pre-existing database of the two studies.

Definitions

Abnormal blood test results (e.g., elevated LDH or β-2 microglobulin) were defined as being above the upper limit of normal at the individual centre. Many patients had received previous therapy, and therefore the Ann Arbor staging criteria was considered to be inappropriate. 'Limited extent of disease' was thus defined as 'involvement of one or more lymph node regions on the same side of the diaphragm, or localised involvement of an extralymphatic organ or site'; all others were considered to have extensive disease. Most patients in this analysis had extensive disease. 'Bulk' disease was defined as >10 cm at one or more measurable sites.

Recurrent disease was defined as that previously responsive to treatment (i.e., PR or CR to the last chemotherapy regimen), while *refractory* disease was defined as the failure to respond (i.e., SD or PD) to the last treatment. Three patients received treatment following an incomplete response to their last treatment (i.e., in PR), and the indication for therapy for these three was considered to be 'consolidation of prior response'.

Among the previously-treated patients, the preceding treatments were categorised generally as: 'Alkylating agents' (chlorambucil, or cyclophosphamide, vincristine and prednisolone-'CVP'); anthracycline-based regimens (combination chemotherapy including doxorubicin, most commonly 'CHOP' or 'CHVP'); fludarabine phosphate; or consolidative high-dose therapy (with autologous haematopoietic support).

Strict response criteria were applied, using the sum of bidimensional measurements of measurable lesions, and all responses were confirmed one month later, in accordance with WHO response criteria. Briefly, a *complete response* (CR) was defined as the complete resolution of any evidence of MCL, with no residual lymphadenopathy $\geqslant 1$ cm^2; *partial response* (PR) was defined as a $>50\%$ decrease in measurable lesions as noted above, and a $>50\%$ decrease in 'unmeasurable' lesions (e.g., bone marrow (BM) infiltration); *stable disease*, a $\leqslant 50\%$ decrease in MCL, or $\leqslant 25\%$ increase, measured as under 'PR'; and *progressive disease*, (PD) a $\geqslant 25\%$ increase in disease, or the development of any new manifestations of MCL.

Statistical considerations

In order to determine which factors at the time of treatment were associated with response (PR and CR), an analysis was performed including the factors listed in Table 2. Statistical modeling was performed by ordered logistic regression [13], using the four possible outcomes to treatment (CR, PR, SD, or PD). Model building was performed by first assessing significant univariate factors ($P \leqslant 0.05$), then forming a multivariate model consisting of these, adding or subtracting terms as were or were not influential. A β coefficient above zero is associated with a lower response rate (RR), while a β coefficient below zero is associated with a higher response rate.

The duration of response, time to progression (TTP), and survival following Rituximab were calculated according to the method of Kaplan and Meier [14]. The duration of response was calculated from the date of response (CR and PR) to the date of progression. The time to progression (TTP) was measured from the start of treatment until progression of MCL, including all patients who had a response, and those in whom treatment failed (SD and PD). Patients were censored in the latter two analyses at the time of further therapy for MCL if given prior to disease progression [e.g., if given as consolidation of response following Rituximab (patients achieving CR and PR), or to induce a response following failure of the treatment (patients achieving

Table 2. Factors analysed in relation to response to Rituximab, and significance using ordered logistic regression (n = 81).

Factor	n	Univariate P-value	β coefficient	SE
Univariate				
Elevated LDH	26	0.004	1.44	0.50
Prior alkylating agents	26	0.01	1.26	0.50
Performance status = 2	13	0.02	1.53	0.65
Refractory disease	22	0.04	1.09	0.52
Prior fludarabine phosphate	12	0.04	1.20	0.59
Splenomegaly	34	0.05	0.89	0.45
Gastrointestinal involvement	10	0.06	1.18	0.63
Bulk disease	36	0.07	0.79	0.43
Age at treatment	N/A	0.21	0.03	0.02
Elevated β-2 microglobulin	31	0.23	0.63	0.52
Prior high-dose therapy	7	0.30	0.81	0.78
Extensive disease	76	0.37	−0.82	0.91
No. of previous treatments	N/A	0.47	0 48	0.57
Prior anthracycline	31	0.51	0.28	0.43
Leukaemic phase	24	0.64	0.22	0.46
Dose and schedule	N/A	0.85	0 13	0.67
Blastic histologic variant	12	0.89	0.08	0.60
Bone-marrow infiltration	65	0.93	0.04	0.45
Multivariate				
Elevated LDH		0.007	1.36	0.51
Alkylating agents		0.03	1.09	0.50

Abbreviations: SE – standard error of the β coefficient; N/A – measured as a continuous variable, and therefore 'not applicable'.

SD)]. Differences in the duration of response and TTP between groups were analysed for statistical significance using the log-rank test. Survival was calculated from the start of treatment until death, including all 87 patients. Patients were censored at last follow-up in each of the analyses if the event (i.e., PD or death, respectively) had not yet occurred.

Results

Response

A response was achieved in 30 patients (CR, n = 11; PR, n = 19). Six patients did not complete therapy, and treatment failed in the remaining 51 (SD, n = 33; PD, n = 18). The overall RR was therefore 34% (30 of 87). Considering only evaluable patients (n = 81), the RR was 37%, and was the same for patients with both MCL1 and MCL2. The CR rate was 14%.

Analysis of factors associated with response

On univariate analysis, several factors at the time of treatment were associated with a significantly lower RR (Table 2), including: Elevated LDH (P = 0.004); refractory disease (P = 0.04); PS of two (P = 0.04); and splenomegaly (P = 0.05). Previous therapy with either alkylating agents, or with fludarabine phosphate, were also associated with a lower RR (P = 0.01 and P = 0.04, respectively). Gastrointestinal tract involvement (P = 0.07) and bulky disease (P = 0.07), had borderline significance. Importantly, MCL1, and Rituximab dose and schedule (500 mg/m^2 vs. 375 mg/m^2, and eight vs. four weeks), were not associated with a higher RR. It must be noted that the number of patients treated with a higher dose or longer course of therapy was relatively small.

On multivariate analysis, only elevated LDH (P = 0.007) and previous alkylating agents (P = 0.03) retained statistical significance.

Duration of response

Seven of thirty patients were censored in this analysis at the time of further treatment given to consolidate the response achieved with Rituximab, (i.e., prior to MCL progression). At a median follow-up of 1.4 years, 12 patients have developed progressive MCL. The median duration of response was one year.

The duration of response was significantly longer for patients achieving CR vs. PR (P = 0.04) (Figure 1), but not for patients with MCL1 vs. MCL2 (not shown). The median duration of CR has not yet been reached, and the median duration of PR was almost seven months.

Time to progression following Rituximab

Twenty of eighty-one patients were censored in this analysis, at the time of further therapy for MCL prior to documentation of progressive MCL. At a median follow-up from therapy of 1.4 years, 48 patients have developed PD. The median TTP from the start of treatment was seven months (Figure 2). There was no difference between patients with MCL1 vs. MCL2, or for patients with relapsed vs. refractory disease.

Survival

The median survival of patients with MCL2 was 1.7 years, and for those with MCL1 has not yet been reached (not shown).

Discussion

Anti-CD20 monoclonal antibody-based therapy with Rituximab can induce a remission in over one-third of patients with MCL, both newly-diagnosed and previously-treated. Importantly, some (albeit few) patients achieve CR, which in many instances appears to be durable. The treatment of MCL has been unsatisfactory; more intensive anthracycline-based chemotherapy regimens have not been shown to improve survival [4, 15], and high-dose therapy does not appear to offer long-term remission to most patients [16]. New treatments for MCL are needed, and Rituximab is therefore a welcome and important addition.

The CR rate of 14% in this study compares favorably with the experience of Rituximab in follicular lymphoma (CR rate 6%), although the overall RR in MCL was somewhat lower (approximately 50% in follicular lymphoma) [7]. The finding that the RR was similar for both MCL1 and MCL2 was unexpected. This suggests

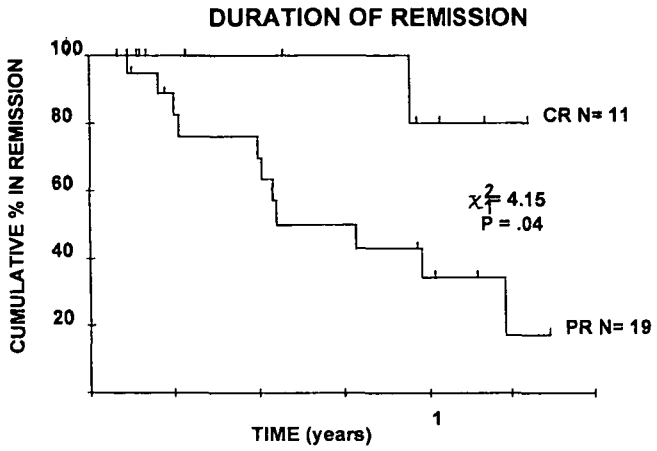

Figure 1 The duration of response for patients achieving CR vs. PR ($P = 0.04$).

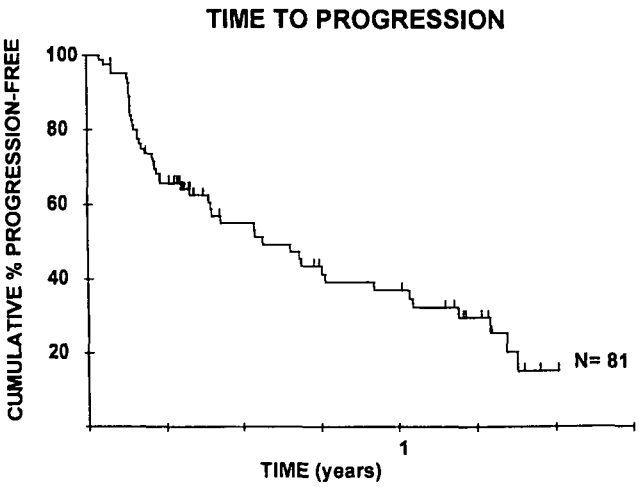

Figure 2. Time to progression from the start of treatment ($n = 81$)

that the activity of Rituximab is not affected by prior exposure to cytotoxic chemotherapy, and that resistance to Rituximab is therefore mediated by some other (unique) mechanism.

Patients previously-treated with alkylating agents had a lower RR (24%). While the import of this is not clear, it must be stressed that this represents a statistical association (and not causation), and that the reasons for prescribing alkylating agents for specific patients with MCL may play a large role in confounding interpretation of this finding. In this study, those treated with alkylating agents were more likely to have refractory disease, to be older, and to have had a greater number of previous treatments. Obviously, then, other factors may be at play, and this result should be treated with caution.

In contrast, it is not surprising that LDH at the time of treatment was closely associated with response. Elevated LDH is an important adverse prognostic factor in both aggressive and indolent NHL [17, 18].

Most patients in this study had extensive disease, and many had other adverse risk factors (e.g., refractory disease, extranodal involvement, elevated β-2 microglobulin, etc.). While adverse prognostic factors are common in MCL [1–4], it is possible that patients with a more favorable prognostic profile (e.g., limited stage disease, normal LDH, etc.) may have a higher RR to Rituximab. It was beyond the scope of this study to determine whether other histological, immunophenotypic, or molecular biological factors (e.g., presence of t(11;14)) had an impact on the response to Rituximab.

The duration of response (median 1 year) was encouraging, and was similar to that seen in follicular lymphoma. However, the TTP gives a more accurate description of the expectations of treatment for the larger group of evaluable patients. The median TTP of only seven months for both MCL1 and MCL2 was disappointing. The fact that all of the patients with PD following therapy are included in the analysis of TTP, while 20 patients (including seven who achieved a response) were censored at the time of further therapy, suggests that this is maybe a conservative estimate. However, the relentless pattern of progression (Figure 2), and the persistent decline in survival evident following treatment, suggests that Rituximab will not significantly alter the clinical course of the disease. Single agent Rituximab does not therefore represent a cure for MCL, but instead may offer significant benefit in the palliative setting.

The activity of Rituximab, and in particular the ability to induce a complete response in some patients, suggests a future role for its use in the treatment of MCL. Studies of Rituximab in combination with cytotoxic chemotherapy in other subtypes of NHL have demonstrated high complete response rates with (generally) acceptable toxicity [19, 20]. Combination studies in MCL to test that hypothesis are now appropriate.

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*Appendix

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