Activity and safety profile of low-dose rituximab for the treatment of autoimmune cytopenias in adults

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ABSTRACT

We conducted a retrospective analysis of 11 consecutive patients with various autoimmune cytopenias who failed to respond to conventional treatments and received a fixed-dose regimen of rituximab (100 mg weekly for 4 consecutive weeks). Sustained complete responses were achieved in 4 out of 7 patients with idiopathic thrombocytopenic purpura and in 1 patient with autoimmune pancytopenia. A partial response was observed in 1 patient with autoimmune hemolytic anemia. The immunotherapy had no effect in 1 patient with pure red cell aplasia or in 1 patient with autoimmune neutropenia. No infusion-related or delayed toxicities attributable to rituximab were experienced by any of the patients.

Key words: autoimmune disease, cytopenias, rituximab, low dose

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Selective B-cell depletion with rituximab, a chimeric anti-CD20 monoclonal antibody, has been shown to have significant activity in the treatment of immune disorders resulting from autoantibodies, including hematologic disorders such as autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenic purpura (ITP), autoimmune neutropenia (AIN), acquired hemophilia, and pure red cell aplasia (PRCA).[1]

In most studies, the drug was generally used at the doses developed and licensed for the treatment of B cell non-Hodgkin's lymphoma (NHL), 375mg/m^2 weekly for 4 consecutive weeks. However, the tumor burden in lymphomas is often high whereas in ITP and other autoimmune hematologic disorders the B cell mass is presumably normal. We therefore hypothesized that a much smaller dose (100 mg fixed dose) could still be effective in autoimmune cytopenias. Furthermore, it was assumed that such low doses could also be associated with a lower incidence of first-infusion reactions, which are known to be the most common adverse event related to the drug.[2] In this paper we report the activity and safety profile of attenuated doses of rituximab for the treatment of adults with autoimmune cytopenias refractory to conventional treatments.

Design and Methods

Study design

We conducted a retrospective analysis of data from 11 consecutive patients with autoimmune cytopenias, 6 of whom have been treated at The Royal London Hospital, U.K., and 5 at Regina Apostolorum Hospital, Albano Laziale and the University of Rome *Tor Vergata*. Approval from the local hospital ethics committee and patients' informed consent were obtained for Italian patients only, since in the U.K. rituximab is considered part of local standard practice for immunohematologic patients who fail other therapies.

Treatment consisted of rituximab (MabThera, Roche®) administered intravenously (IV) at a dose of 100 mg weekly for 4 consecutive weeks (total dose per patient 400 mg, irrespective of body surface area).

Table 1. Clinical characteristics of 11 patients with autoimmune cytopenia at the time of rituximab therapy.

UPN	*Country*	*Age (yrs)*	*Sex*	*Diagnosis*	*Detectable autoantibodies*	*Prior therapies*	*Duration of disease (months)*
1	Italy	32	F	ITP	PAIg	P, Ig	8
2	Italy	41	F	ITP	PAIg	P, Ig	17
3	Italy	25	M	ITP	PAIg	P, Ig, DXM	9
4	Italy	20	F	ITP	PAIg	P, Ig	33
5	Italy	58	M	ITP	PAIg, ANA	P, Ig, Az	17
6	UK	44	F	ITP	PAIg	Ig, aRh, Az, P, MMF	60
7	UK	27	F	ITP	PAIg	P, aRh, Az	14
8	UK	81	F	PRCA	ANA, ASMA, AACHR	P, Az, CyA, MMF	72
9	UK	30	F	AIN	NAA, RF	G-CSF	108
10	UK	47	F	AIHA	DAT	P, Ig	11
11	UK	64	F	AIPC	DAT, NAA, PAIg, RF	G-CSF, Ig	1

UPN: unique patient number; ITP: idiopathic thrombocytopenic purpura; PRCA: pure red cell aplasia; AIN: autoimmune neutropenia; AIHA: autoimmune hemolytic anemia; AIPC: autoimmune pancytopenia; PAIg: platelet-associated immunoglobulins; RF: rheumatoid factor; ANA: antinuclear antibodies; DAT: direct antiglobulin test; NAA: neutrophil-associated antibodies; AACHR: anti-acetylcholine receptor antibodies; ASMA: anti-smooth muscle antibody; P: prednisone; Ig: intravenous immunoglobulin; DXM: high-dose dexamethasone; aRh: anti-Rh immunoglobulin; MMF, mycophenolate mofetil; G-CSF: granulocyte-colony stimulating factor.

All patients were given pre-medication comprising hydrocortisone 100 mg IV, chlorpheniramine 10 mg IV, and oral paracetamol 1 gram, 1 hr. prior to each infusion to minimize any infusional reactions.

Patients

Patients' clinical and laboratory characteristics are summarized in Table 1. There were 9 women and 2 men (median age 41 years, range 20–81 years). Patients from the U.K. had a variety of autoimmune cytopenias including ITP (n=2), AIHA (n=1), PRCA (n=1), AIN (n=1), and autoimmune pancytopenia (AIPC, n=1). Those from Italy all had ITP. The median disease duration was 17 months (range 1-108 months), and the median number of previous therapies was 2 (range 1-5).

Patients were not considered eligible for rituximab therapy if they had active bacterial or viral infections, or positive hepatitis B and C serology.

Laboratory studies

Laboratory evaluation before enrollment included: complete hemogram, serum chemistry profiles, direct and indirect Coombs' test, prothrombin time, partial thromboplastin time, fibrinogen levels, and serologic tests for hepatitis B and C, HIV, cytomegalovirus, and toxoplasmosis. Monitoring of patients included a weekly hemogram. The frequency of hemograms could be reduced at the clinician's discretion upon achievement of a response. For the single patient with AIHA, additional tests included the reticulocyte count, lactate dehydrogenase (LDH) levels, and bilirubin levels.

The determination of lymphocyte subsets and of serum immunoglobulin levels were systematically evaluated only in Italian ITP patients. These patients were assessed before the first rituximab infusion, after 1 month, 2 months, and every 2 months thereafter.

Response criteria

There are no published guidelines on response criteria in autoimmune cytopenias. Those reported here have been elaborated on previously published reports. A complete platelet response (CR) was defined as an increase in platelet counts to >150×10^9/L on two consecutive occasions.[3] A partial response (PR) was defined as an increase in the platelet count to between 50 and 150×10^9/L on two consecutive occasions, 1 week apart. Duration of response was considered from the day of the initial infusion to the first time of relapse (platelet count <30×10^9/L) or to time of analysis (31 March 2007).

Criteria for CR in AIHA were resolution of both anemia (Hb >12g/dL) and signs of hemolysis off all therapy for at least 4 weeks after rituximab treatment.[4] A PR was defined as a stable increase in hemoglobin level of at least 2 g/dL and discontinuation of concomitant therapy.

A definition of response for AIN was at least 100% increase and an absolute increase >0.5×10^9/L of the neutrophil count.[5]

Response in PRCA was defined as an increase of hemoglobin concentrations to >11 g/dL, re-establishment of erythropoiesis (erythroid precursors <10% of marrow nucleated cells), and independence from transfusion. Partial response was as above, but with hemoglobin <11 g/dL.[6]

Results

Hematologic responses

Details about the blood cell counts prior to and after rituximab therapy are provided in Table 2.

Complete responses were seen in 4 out of the 7 patients with chronic ITP. In 2 of the responders (cases 1 and 5), there was an early rise in platelet count after the first rituximab infusion. The time to maximum response ranged from 6-12 weeks. One patient from the UK series

Table 2. Hematologic responses to rituximab therapy.

UPN/ diagnosis	Pre-rituximab hemogram			Post-rituximab hemogram			Time to maximum response* (weeks)	Duration of response (months)	Additional therapy during the study period
	Hb (g/dL)	ANC ($\times 10^9$/L)	Plts ($\times 10^9$/L)	Hb (g/dL)	ANC ($\times 10^9$/L)	Plts ($\times 10^9$/L)			
1/ITP	13.3	4.2	17	12.8	3.3	341	6	14+	P
2/ITP	11.9	4.5	19	11.6	4.7	20	–	–	P
3/ITP	14.7	5.3	3	14.5	5.6	11	–	–	P
4/ITP	12.5	3.8	13	12.0	3.1	278	6	12+	P
5/ITP	15.6	6.1	22	15.1	4.6	310	8	10+	P
6/ITP	11.1	3,7	9	12.5	2.9	230	12	6†	P
7/ITP	10.2	4.3	9	10.5	4.0	16	–	–	MMF
8/PRCA	10.6‡	3.4	189	10.3‡	3.3	175	–	–	–
9/AIN	11.5	0.7	243	11.4	0.9	215	–	–	G-CSF
10/AIH	7.6	4.1	217	9.7	3.9	198	12	8+	–
11/AIPC	8.7	0.5	26	12.7	2.5	302	17	14+	G-CSF

*UPN: unique patient number; ITP: idiopathic thrombocytopenic purpura; PRCA: pure red cell aplasia; AIN: autoimmune neutropenia; AIHA: autoimmune hemolytic anemia; AIPC: autoimmune pancytopenia; Hb: hemoglobin concentrations; ANC: absolute neutrophil count; Plts: platelet count; P: prednisone; MMF: mycophenolate mofetil; G-CSF: granulocyte-colony stimulating factor. *From first rituximab infusion; †this patient went abroad and was lost to follow-up; ‡this patient received 3 weekly transfusions. The transfusion need remained the same after rituximab therapy.*

was lost to follow-up after 6 months from the first rituximab infusion while still in CR. Three other patients maintain their remission status at last follow-up, with follow-up times ranging from 7-14 months.

As far as other autoimmune cytopenias are concerned, we observed a complete response in the patient with AIPC (Figure 1) and a partial response in the patient with AIHA. Rituximab therapy had no effect in the patient with PRCA or in the patient with AIN.

Safety profile

Low dose rituximab was well tolerated in all 11 patients, with no infusion reactions. No infections occurred during therapy. Mild respiratory tract infections (grade 1, according to the National Cancer Institute criteria)[7] occurred in responding patients for up to a year thereafter

Monitoring of immunologic parameters

Circulating CD19-positive B cells fell to $<0.03\times10^9$/L within 4 weeks in the 5 patients measured at this time point. In 3 continuously responding patients, B-cell recovery occurred between 6 and 10 months. Median absolute T-cell counts in peripheral blood, using CD3, CD4 and CD8 and natural killer cell counts, remained stable during the study period.

All patients had normal immunoglobulin G (IgG) or IgM levels before rituximab, and maintained normal levels after rituximab.

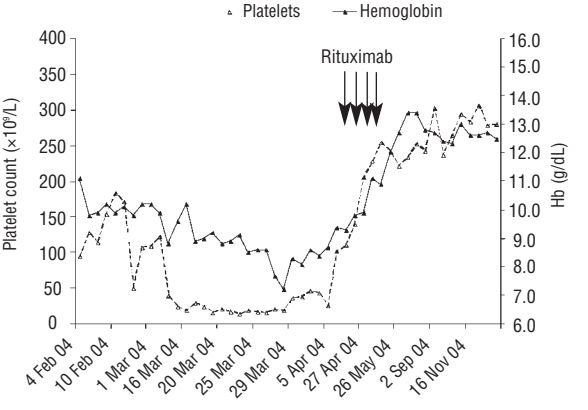

Figure 1. Time course of platelet and hemoglobin counts in the patient with autoimmune pancytopenia (case 11). The neutrophil response is not shown on this graph. However, pre-rituximab therapy her neutrophils were $<0.5\times10^9$/L despite daily G-CSF. One day after the first infusion of rituximab her neutrophils rose to 2.5×10^9/L and has remained $>2.0\times10^9$/L since the time of this report.

Discussion

The main objective of our retrospective analysis was to investigate the activity of rituximab in autoimmune cytopenias at doses much lower than those used in patients with lymphoma. A fixed dose of 100 mg weekly for 4 times (total dose 400 mg) was chosen in our study arbitrarily but with a rationale, since 100 mg represents the smallest single-dose vial of rituximab available. In spite of all the limitations of a small case series, our results are promising and give relevant indications for the design and interpretation of future trials with rituximab.

This study shows that: (i) low dose rituximab can produce significant and durable responses which are associated with B cell depletion; (ii) the reduced intensity immunotherapy may possibly have a more favorable side-effect profile than the standard doses; (iii) the costs associated with the low dose treatment are considerably lower than those associated with standard dose treatment. A complete and durable response was observed in 4 out of 7 (57%) patients with chronic ITP, who made up

most of our study cohort. This is what would have been expected with conventional dosing, which produces an overall response (complete + partial) in around 60% of patients and responses longer than 1 year in no more than 40% of patients.[3,8] Immunologic studies, and in particular the B cell count, were only carried out in Italian ITP patients. B cell depletion was observed in all cases, and the duration of B cell depletion in responding patients appeared comparable to that observed with standard doses of the drug.[3,9] This finding supports our hypothesis that the dose required for patients with normal B cell numbers is less than the lymphoma dose.

It is clear from published data that there is considerable toxicity associated with the treatments in current use.[10] In our series, the drug was not associated with adverse events, particularly with first infusion reactions. However, the relatively short follow-up of our patients and the non-randomized nature of this study prevents us from drawing definite conclusions about the safety profile of the drug.

Because of the relatively high costs of the drug, it is current practice for most units, particularly in the UK, to use rituximab only when all other treatment strategies have failed. If low dose rituximab is as effective as our study suggests, this treatment may be a relatively cheap option which would be easily affordable by even the most hard pressed hospitals.

Given that the number of patients we treated was small and the group comprised a mixture of different types of cytopenias, it remains to be seen whether our data can be reproduced. A trial is required involving a much larger number of patients with refractory autoimmune disease, preferably comparing standard with low dose rituximab. However, despite the size of our study, it does suggest that low dose rituximab offers a further treatment option for this difficult group of patients in whom the toxicities of standard treatment greatly outweigh any minor benefits they might gain.

Authors' Contributions

DP, SA, ACN and RS are responsible for the working hypothesis, designing the study, and writing the article; DP and RS interpreted and analyzed data; TB and MLE are responsible for clinical care of patients, management and analyses of all hematologic and clinical data, analyses and assessment of hematologic and non-hematologic toxicity. All authors took part in the revision of the manuscript and approved the final version.

Conflicts of Interest

The authors reported no potential conflicts of interest.

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