Int J Hematol (2010) 92:283–288
DOI 10.1007/s12185-010-0635-4

ORIGINAL ARTICLE

Rituximab in immune thrombocytopenia: transient responses, low rate of sustained remissions and poor response to further therapy in refractory patients

Aamer Aleem · Ahmed S. Alaskar · Farja Algahtani · Mushtaq Rather · Muhamad Hitham Almahayni · Abdulkarim Al-Momen

Received: 13 February 2010 / Revised: 8 June 2010 / Accepted: 29 June 2010 / Published online: 17 July 2010

Abstract Management of patients with immune thrombocytopenia (ITP) refractory to standard treatment is difficult. Recent studies show that rituximab, a chimeric anti-CD20 monoclonal antibody, is useful in the treatment of ITP. We retrospectively studied 24 patients who received 29 rituximab treatments for relapsed or refractory ITP. Patients had received a median of 3 treatment regimens before (range 1–8) and 11 patients had prior splenectomy. Responses were achieved in 19 of 29 (66%) treatments. The median time to response was 3 weeks (range 1–20) from the start of therapy and median duration of response was 13 weeks (range 1 week–55 months). Responses were mostly short lived and after a median follow-up of 22 months (range 2–70), 10 (34%) responses were sustained after 6 months, 7 (24%) responses sustained after 1 year and only 5 patients continued to have a response at last visit after 8, 10, 24, 30 and 54 months of follow-up. Previous splenectomy was associated with a poor response ($p = 0.034$). Patients who failed rituximab and had prior multiple treatments including splenectomy, had a poor outcome of further therapies. We conclude that rituximab is well tolerated and is useful in some patients with relapsed or refractory ITP; however, only about one-fifth of patients achieved sustained remissions. Patients refractory to rituximab had a poor response to further treatment.

Keywords Immune thrombocytopenia · ITP · Adults · Platelets · Rituximab

A. Aleem (✉) · F. Algahtani · M. H. Almahayni · A. Al-Momen
The Division of Haematology/Oncology, Department of Medicine (38), College of Medicine and King Khalid University Hospital, King Saud University, P.O. Box 7805, Riyadh 11472, Saudi Arabia
e-mail: aameraleem@hotmail.com

A. S. Alaskar · M. Rather
The Division of Adult Haematology, Department of Oncology, King Abdulaziz Medical City, Riyadh, Saudi Arabia

1 Introduction

Immune (idiopathic) thrombocytopenia (ITP) is a disorder mediated by auto-antibodies against the platelet antigens that accelerate their destruction. Antibody-coated platelets are removed by the reticuloendothelial system, particularly in the spleen. ITP is usually an isolated thrombocytopenic disorder without an associated illness when it is called primary or idiopathic. Immune thrombocytopenia can be secondary to a variety of causes and commonly associated with lymphoproliferative disorders, particularly chronic lymphocytic leukemia (CLL) or a systemic immune disease like systemic lupus erythematosus (SLE) [1]. Significant drop in the platelet count can result in mucocutaneous bleeding of variable severity and is usually clinically manifest in many patients when the platelet count drops below 30×10^9/l [1]. Around 20–30% of adult patients are non-responsive to conventional therapy including steroids, intravenous immunoglobulins (IvIg), anti-D and splenectomy [2]. These patients have a chronic, refractory disease unlikely to be cured, although spontaneous remissions may occur in some patients [3]. This group of patients have a significant risk of bleeding with increased morbidity and mortality [1, 4–7]. Further treatment is recommended in these patients if they have a low platelet count and bleeding symptoms.

Because of better awareness and possibility of newer modalities of treatment, many patients are not willing to

undergo splenectomy and like to try other forms of medical therapy before this procedure. These options usually include various immune modulating agents. Low response rates and significant side effects make the patients and the physicians hesitant to try these modalities of treatment, particularly in younger patients. In view of this, new treatment strategies are needed which are more effective and less toxic.

Rituximab (Mabthera; Roche Pharmaceuticals, Basel, Switzerland) is an anti-CD20 antibody which was originally developed for B cell lymphomas, and has shown excellent activity in various B cell lymphoproliferative disorders [8]. Rituximab is a chimeric, monoclonal antibody that specifically targets CD20 B cell surface antigen. Rituximab effectively reduces circulating B cell count by at least three distinct mechanisms: complement-mediated cytotoxicity, cell-mediated cytotoxicity, and induction of apoptosis [9, 10]. Apart from being effective in B cell lymphomas, rituximab has shown activity in many autoimmune hematological and non-hematological disorders with a favorable safety profile [11–17]. Rituximab has been reported to produce variable responses in patients with ITP and here we describe our experience with 24 adult ITP patients treated with rituximab.

2 Patients and methods

We retrospectively studied adult ITP (primary or secondary) patients who received rituximab for refractory or relapsed disease at two tertiary care centers in Riyadh. All patients had platelet counts less than 30×10^9/l except one patient who had a relapsed but steroid responsive disease (platelet count 37×10^9/l) and received rituximab because of poorly controlled diabetes. All patients gave informed consent. Rituximab was given at a dose of 375 mg/m^2 weekly for a median of 4 doses. Patients received antihistamines, paracetamol and hydrocortisone as premedication prior to rituximab infusion. One patient received rituximab with a presumed diagnosis of ITP but later proved to have May–Hegglin anomaly and was excluded from analysis.

Response to rituximab was assessed weekly for 1 month and 1–3 monthly thereafter. Complete response (CR) was defined as a platelet count of more than 100×10^9/l, partial response (PR) as a platelet count of more than 50×10^9/l but less than 100×10^9/l, minimal response (MR) if the platelet count was $>30 \times 10^9$/l and $<50 \times 10^9$/l and no response if platelet count remained unchanged. Durability of responses was assessed at 6 and 12 months as well as at the last follow-up. The response to further therapies in patients refractory to rituximab, type of therapy and the outcome of these patients was also studied.

Additional information was obtained from the patients' notes and computer records regarding demographic data, age at diagnosis of ITP and the type of previous treatments, age and platelet count at rituximab therapy, timing and type of responses to rituximab, duration of responses and the timing of any relapses.

Data were analyzed using descriptive terms like absolute numbers and percentages, or medians and ranges, as appropriate. Student's t test was used to study the association of response (CR + PR + MR) with clinical parameters, and that of sustained response of >6 months with the type of response (CR or PR + MR). A p value of ≤ 0.05 was considered significant.

3 Results

A total of 24 patients received 29 rituximab treatment courses for ITP. Nineteen patients had primary (idiopathic) disease and five patients had secondary ITP. The median number of previous treatments was 3 (range 1–8) and 11 patients had prior splenectomy. Patient characteristics and treatment details are shown in Table 1.

Responses were achieved in 19 of 29 (66%) treatment courses and rituximab failed in 10 (34%) cases. A CR was achieved in 13 cases (45%) and a PR or MR in 6 (21%) treatments. The median time to response was 3 weeks (range 1–20) from the start of therapy and median duration of response was 13 weeks (range 1 week–55 months). Responses were mostly short lived and after a median follow-up of 22 months (range 2–70), 10 (34%) responses were sustained after 6 months, 7 (24%) responses sustained after 1 year and only 5 patients continued to have responses without relapse at the last visit after 8, 10, 24, 30 and 54 months of follow-up. Only one of these 5 patients with continued responses had prior splenectomy. All 3 patients with CLL-associated ITP responded and one of these patients achieved a second CR post-relapse after re-treatment with rituximab, lasting more than 6 months. Outcome of rituximab therapy and summary of responses are shown in Table 2.

Prior splenectomy was associated with a failure of response ($p = 0.034$) while sustained response of more than 6 months had a borderline correlation ($p = 0.055$) with achievement of CR but this did not reach statistical significance. Seven out of 10 refractory patients had prior splenectomy. Age at rituximab therapy, gender, duration of disease and number of previous treatments did not correlate with response (Table 3).

Outcome of patients refractory to rituximab therapy was generally poor in terms of response to subsequent therapies. Two of the 3 refractory patients underwent

Table 1 Patients' characteristics

Characteristics	Patients' values
Patient number	24
Total number of treatments	29
Age (years)	
Median	33
Range	14–70
Gender	
Female	16
Male	8
No of previous treatments	
Median	3
Range	1–8
Type of previous treatments	
Steroids	24/24
IvIg	16/24
Splenectomy	11/24
Other treatments	12/24
Time from ITP diagnosis (months)	
Median	36
Range	1–240
Time from splenectomy to rituximab therapy (months)	
Median	114
Range	24–216
Platelet count at rituximab therapy ($\times 10^9$/l)	
Median	13
Range	3–37
Associated disease	
Idiopathic	19
CLL	3
NHL	1
SLE	1

Table 2 Summary of results

Parameter	Results
Response	
CR	13 (45%)
PR and MR	6 (21%)
NR	10 (34%)
Time to response (weeks)	
Median	3
Range	1–20
Duration of response	
Median	13 weeks
Range	1 week–55 months
Durable responses	
At 6 months	10 (34.5%)
At 12 months	7 (24%)
Sustained (till last follow-up)	5 (17%)

Table 3 Comparison of some clinical parameters with response

Parameter[a]	Patients	OR (CR + PR + MR)	NR	*p*
Gender				
Male	8	5	3	
Female	16	9	7	0.68
Age (years)				
≤40	14	8	6	
>40	10	6	4	0.42
Time since diagnosis (years)				
≤1	9	3	6	
>1	15	7	8	0.54
≤5	16	11	5	
>5	8	3	5	0.22
No. of previous treatments				
≤2	9	6	3	
>2	15	7	8	0.32
No splenectomy	13	9	4	
Splenectomy	11	4	7	0.032
Sustained response (months)				
>6	10	7 (CR)[b]	3 (PR + MR)[b]	
<6	9	6	3	0.055

OR overall response, *NR* no response

[a] Parameters compared to response (any response = CR + PR + MR) are given as headings and the variables compared within the parameter given to the right and below

[b] Sustained response of >6 months compared to CR or PR + MR separately

splenectomy without a response. Other types of treatment used in refractory patients included steroids, IvIg, azathioprine, mycophenolate, vincristine, danazol and romiplostim. These patients received a median of 2 treatments (range 1–4) after rituximab failure. The median platelet count of this group at the time of last follow-up was 16×10^9/l (range 6–128) with 7 out of 10 patients having a platelet count below 30×10^9/l. One of the patients in this group died 2 years after receiving rituximab. The cause of death (renal failure) in this patient was considered to be unrelated to ITP or rituximab therapy.

The adverse events related to rituximab therapy were generally mild. Seven (29%) patients had minor infusion related or subsequent reactions in the form of transient hypotension, palpitations, fever, and skin rashes. One patient with CLL who received rituximab therapy twice, required stopping and delaying the first infusions both the times due to significant hypotension but none of the patients required termination and cancelation of therapy.

Three patients died: one of renal failure-related complications after 24 months and 2 patients with CLL-associated ITP died of progression of the CLL 15 and 18 months post-rituximab treatment. Cause of death was not considered to be related to rituximab therapy or ITP in any of these patients.

4 Discussion

The anti-CD20 monoclonal antibody rituximab has been used to treat chronic ITP patients with variable responses [18–20]. Rituximab produced an initial response in approximately 40–60% of cases and sustained responses were observed in 35–67% of patients [21–25]. The results of our study, largest from the middle east, show that responses were achieved in two-third of the patients, similar to other published reports, but responses were mostly short lived and sustained responses were achieved only in about one-fifth of the patients. Schweizer and colleagues reported low rate of sustained responses in 14 patients. Response duration was short (8 weeks) and only around 20% of patients maintained responses beyond 6 months [26]. The results of long-term responses in our study are similar to those reported by Schweizer et al. and are in contrast with most of the other published reports. It is difficult to comment on the cause(s) of inferior long-term results in our study but this is likely to be due to diverse patient characteristics and disease etiology. It appears that the pathogenesis of ITP is heterogeneous with multiple mechanisms operating in different patients or even in the same patient [27]. The heterogeneity of pathogenesis along with differences in patient characteristics and criteria used for reporting responses and clinical outcomes in ITP, as described by Ruggeri et al. [28], is the possible explanation for conflicting results in some of the published reports.

Factors predictive of initial and long-term response to rituximab treatment in ITP patients have not been clearly identified and no clinical or biochemical parameters were consistently associated with outcome following rituximab therapy. Some of the factors reported to be associated with poor response include older age, failure to achieve a complete response, a delayed response, long standing disease, previous splenectomy, and heavy treatment with multiple regimens prior to rituximab therapy [20, 21, 23, 24, 29]. Splenectomy was associated with a poor response in our patients and 4 out of 5 patients with continued sustained remission at the last follow-up were non-splenectomized. Better responses to rituximab in non-splenectomized patients have been observed by some investigators [24]. One small study found better responses in splenectomised patients [26] while others did not report any correlation between response and splenectomy status [20, 25, 30]. No study has directly compared rituximab to splenectomy in patients with chronic ITP but such a study would be difficult to conduct because of involvement of a surgical procedure.

There is not much information available about heavily pretreated ITP patients who fail rituximab therapy and only few studies have reported the outcome of such patients [31].

In our study, the outcome of patients refractory to rituximab therapy was poor in terms of response to further therapy. It is possible that ITP patients who have long duration of disease and multiple previous therapies including splenectomy and fail rituximab, may be resistant to further therapies. A recent prospective study by Godeau et al. [29] reported results of rituximab use in ITP patients early in the course of the disease as a splenectomy-sparing agent after failure of first line therapy. Sustained responses were achieved in 33% of patients after 2 years and a younger age at the time of therapy was associated with a better response. It is interesting to note that 25 non-responders to rituximab subsequently underwent splenectomy and 15 (60%) of these patients responded to this treatment. Based on these results, it appears that early use of rituximab in the course of chronic ITP may be more effective and spare or delay splenectomy in some patients [21, 29]. Rituximab refractory or relapsed patients can still be expected to benefit from splenectomy. This conclusion is congruent with other lines of evidence suggesting that rituximab may be more effective in patients with a short duration of disease possibly as a result of the reversion of T cell abnormalities following depletion of the $CD20^{+}$ B cell pool [32]. The observations by Godeau et al. will fuel the debate about the timing of rituximab in chronic ITP, but randomized controlled trials (RCTs) are needed to establish a definitive role for early rituximab administration in non-splenectomized ITP patients [33].

Rituximab also appears to be promising in secondary ITP associated with CLL [24, 34, 35]. Our report included 3 patients with CLL-associated secondary ITP. All the 3 patients responded to rituximab: two patients had complete responses and one patient had a partial response and one of these patients achieved a sustained response beyond 1 year. We believe that these responses were solely due to an independent effect of rituximab on ITP, as the drug was given alone to all 3 patients at the time of ITP diagnosis, although a secondary response due to effect on disease process contributing to platelet count improvement is possible and cannot be ruled out. Peñalver et al. [24] reported 14 patients with CLL-associated ITP treated with rituximab and response rates in these patients were similar to those with idiopathic disease. Our report reiterates the usefulness of rituximab therapy in this setting.

In conclusion, rituximab was well tolerated and achieved responses in two-thirds of relapsed or refractory ITP patients but sustained responses were achieved in only around one-fifth of the patients. Prior splenectomy was associated with a poor response and the outcome of patients refractory to rituximab treatment was poor in terms of further therapy. Rituximab can be useful in some patients with ITP and should be considered in patients with contraindications to, or not willing to undergo splenectomy. Controlled studies are needed to establish a definitive role for early rituximab administration in non-splenectomized ITP patients.

Conflict of interest statement None.

References

1. Cines DB, Blanchette V. Idiopathic thrombocytopenic purpura. N Engl J Med. 2002;364:995–1008.
2. Cines DB, Bussel JB. How I treat idiopathic thrombocytopenic purpura (ITP). Blood. 2005;106(7):2244–51.
3. Simanek R, Panzer S, Lechner K, Pabinger I. Late spontaneous remissions in severe adult autoimmune thrombocytopenia. Ann Hematol. 2007;86:705–10.
4. Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. Arch Intern Med. 2000;160:1630–8.
5. McMillan R. Therapy for adults with refractory chronic autoimmune thrombocytopenic purpura. Ann Int Med. 1997;126:307–14.
6. Stasi R, Stipa E, Masi M, Cecconi M, Scimò MT, Oliva F, Sciarra A, Perrotti AP, Adomo G, Amadori S, et al. Long-term observation of 208 adults with chronic idiopathic thrombocytopenic purpura. Am J Med. 1995;98:436–42.
7. Picozzi VJ, Roeske WR, Creger WP. Fate of therapy failure in adult idiopathic thrombocytopenic purpura. Am J Med. 1980; 69:690–4.
8. Cvetkovic RS, Perry CM. Rituximab: a review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Drugs. 2006;66:791–820.
9. Di Gaetano N, Cittera E, Nota R, Vecchi A, Grieco V, Scanziani E, Botto M, Introna M, Golay J. Complement activation determines the therapeutic activity of rituximab in vivo. J Immunol. 2003;171:1581–7.
10. Golay J, Gramigna R, Facchinetti V, Capello D, Gaidano G, Introna M. Acquired immunodeficiency syndrome-associated lymphomas are efficiently lysed through complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity by rituximab. Br J Haematol. 2002;119:923–9.
11. Robak T. Monoclonal antibodies in the treatment of autoimmune cytopenias. Eur J Haematol. 2004;72:79–88.
12. Stasi R, Stipa E, Forte V, Meo P, Amadori S. Variable pattern of response to rituximab treatment in adults with chronic idiopathic thrombocytopenic purpura. Blood. 2002;99:3872–3.
13. Zecca M, Nobili B, Rameghi U, Perrotta S, Amendola G, Rosito P, Jankovic M, Pierani P, De Stefano P, Bonora MR, Locatelli F. Rituximab for the treatment of refractory autoimmune hemolytic anemia in children. Blood. 2003;101:3857–61.
14. Leandro MJ, Cambridge G, Edwards JC, Ehrenstein MR, Isenberg DA. B-cell depletion in the treatment of patients with systemic lupus erythematosus: a longitudinal analysis of 24 patients. Rheumatology (Oxford). 2005;44:1542–5.
15. Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, Stevens RM, Shaw T. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med. 2004;350:2572–81.
16. Franchini M, Veneri D, Lippi G, Stenner R. The efficacy of rituximab in the treatment of inhibitor-associated hemostatic disorders. Thromb Haemost. 2006;96(2):119–25.
17. Kimby E. Tolerability and safety of rituximab (MabThera). Cancer Treat Rev. 2005;31:456–73.
18. Stasi R, Pagano A, Stipa E, Amadori S. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adults with chronic idiopathic thrombocytopenic purpura. Blood. 2001;98(4):952–7.
19. Giagounidis AA, Anhuf J, Schneider P, Germing U, Söhngen D, Quabeck K, Aul C. Treatment of relapsed idiopathic thrombocytopenic purpura with the anti-CD20 monoclonal antibody rituximab: a pilot study. Eur J Haematol. 2002;69(2):95–100.
20. Cooper N, Stasi R, Cunningham-Rundles S, Feuerstein MA, Leonard JP, Amadori S, Bussel JB. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura. Br J Haematol. 2004;125(2):232–9.
21. Zaja F, Vianelli N, Battista M, Sperotto A, Patriarca F, Tomadini V, Filì C, Tani M, Baccarani M, Fanin R. Earlier administration of rituximab allows higher rate of long-lasting response in adult patients with autoimmune thrombocytopenia. Exp Hematol. 2006;34:571–2.
22. Garcia-Chavez J, Majluf-Cruz A, Montiel-Cervantes L, Esparza MG-R, Vela-Ojeda J, Mexican Hematology Study Group. Rituximab therapy for chronic and refractory immune thrombocytopenic purpura: a long-term follow-up analysis. Ann Hematol. 2007;86:871–7.
23. Arnold DM, Dentali F, Crowther MA, Meyer RM, Cook RJ, Sigouin C, Fraser GA, Lim W, Kelton JG. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med. 2007;146:25–33.
24. Peñalver FJ, Jiménez-Yuste V, Almagro M, Alvarez-Larrán A, Rodríguez L, Casado M, Gallur L, Giraldo P, Hernández R, Menor D, Rodríguez MJ, Caballero D, González R, Mayans J, Millán I, Cabrera JR, Multi-institutional Retrospective Spanish Study Group on the use of rituximab in refractory ITP. Rituximab in the management of chronic immune thrombocytopenic purpura: an effective and safe therapeutic alternative in refractory patients. Ann Hematol. 2006;85(6):400–6.
25. Braendstrup P, Bjerrum OW, Nielsen OJ, Jensen BA, Clausen NT, Hansen PB, Andersen I, Schmidt K, Andersen TM, Peterslund NA, Birgens HS, Plesner T, Pedersen BB, Hasselbalch HC. Rituximab chimeric anti-CD20 monoclonal antibody treatment for adult refractory idiopathic thrombocytopenic purpura. Am J Hematol. 2005;78(4):275–80.
26. Schweizer C, Reu FJ, Ho AD, Hensel M. Low rate of long-lasting remissions after successful treatment of immune thrombocytopenic purpura with rituximab. Ann Hematol. 2007;86(10):711–7.
27. Cines DB, Bussel JB, Liebman HA, Luning Prak ET. The ITP syndrome: pathogenic and clinical diversity. Blood. 2009; 113(26):6511–21.
28. Ruggeri M, Fortuna S, Rodeghiero F. Heterogeneity of terminology and clinical definitions in adult idiopathic thrombocytopenic purpura: a critical appraisal from a systematic review of the literature. Haematologica. 2008;93:98–103.
29. Godeau B, Porcher R, Fain O, Lefrère F, Fenaux P, Cheze S, Vekhoff A, Chauveheid MP, Stirnemann J, Galicier L, Bourgeois E, Haiat S, Varet B, Leporrier M, Papo T, Khellaf M, Michel M, Bierling P. Rituximab efficacy and safety in adult splenectomy candidates with chronic immune thrombocytopenic purpura:

results of a prospective multicenter phase 2 study. Blood. 2008;112:999–1004.
30. Zaja F, Vianelli N, Sperotto A, De Vita S, Iacona I, Zaccaria A, Masolini P, Tomadini V, Tani M, Molinari AL, Baccarani M, Fanin R. B-cell compartment as the selective target for the treatment of immune thrombocytopenias. Haematologica. 2003;88(5):538–46.
31. Dierickx D, Verhoef G, Van Hoof A, Mineur P, Roest A, Triffet A, Kentos A, Pierre P, Boulet D, Bries G, Lê PQ, Janssens A, Delannoy A. Rituximab in auto-immune haemolytic anaemia and immune thrombocytopenic purpura: a Belgian retrospective multicentric study. J Intern Med. 2009;266(5):484–91.
32. Stasi R, Del Poeta G, Stipa E, Evangelista ML, Trawinska MM, Cooper N, Amadori S. Response to B-cell depleting therapy with rituximab reverts the abnormalities of T-cell subsets in patients with idiopathic thrombocytopenic purpura. Blood. 2007;110:2924–30.
33. Warkentin TE, Arnold DM. "Spare-spleen-uximab" for chronic ITP. Blood. 2008;112(4):925–6.
34. Oo TH. Rituximab is effective in the treatment of refractory immune thrombocytopenic purpura associated with chronic lymphocytic leukemia. South Med J. 2005;98(12):1227–8.
35. Zaja F, Vianelli N, Sperotto A, Patriarca F, Tani M, Marin L, Tiribelli M, Candoni A, Baccarani M, Fanin R. Anti-CD20 therapy for chronic lymphocytic leukemia-associated autoimmune diseases. Leuk Lymphoma. 2003;44(11):1951–5.