Rituximab Therapy for Chronic Idiopathic Thrombocytopenic Purpura

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ABSTRACT

**Aim of the study:** to evaluate the long-term response to rituximab in patients with chronic and refractory immune thrombocytopenia purpura (TIP) after failure of conventional therapy, and study response to retreatment with rituximab. **Material and methods:** 41 patients with chronic or refractory ITP were registered in hematology department in Tripoli medical center /Libya treated with rituximab. Patients received 375mg/m² of rituximab weekly for 4 weeks. Response was defined as platelets increase to more than 50x10⁹/l. **Results:** 41 patients were included in this study. Mean age was 42 years. 32/41(78%) were female and 9/41(22%) were males. Mean platelets count before rituximab was 26x10⁹/l, mean platelets count after rituximab treatment 115x10⁹/l. (46.5%) of patients had complete response , (12%) had partial response and (41.5 %) had no response. 5 patients of previously responder had received repeated dose of rituximab,3/5(60%) showed complete response and 2/5 (40%) has no response. Rituximab was well tolerated and show relatively short-term toxicity. **Conclusion:** rituximab is a long term safe and effective alternative treatment for chronic ITP patients. Repeated dose can be used in previously responding patients.

**Keywords:** Immune thrombocytopenic, Rituximab, Response

1. **INTRODUCTION**

Immune thrombocytopenic purpura (ITP) is an immune-mediated disorder in which auto antibody coated platelets are destroyed by opsonization in reticuloendothelial system [1,2,3,4]. It promotes premature destruction of platelets as a result different grades of peripheral thrombocytopenia and clinical bleeding becomes evident. These autoantibodies also inhibit platelets production by megakaryocyte [5]. If severe thrombocytopenia occurs, mucocutaneous bleeding may ensue. First line treatment of ITP includes intravenous immunoglobulin, intravenous anti D, and steroids [6]. Response to these agents is typically short lived and spontaneous improvement occurs in acute ITP. In case of failure to steroid, splenectomy induces 70% to 80% response rate [7]. However almost 30% of adults with ITP fail to respond to conventional therapies steroids, IV immunoglobulin, splenectomy or immunosuppressive drugs and eventually they develop a chronic refractory ITP [8]. Refractory ITP are defined as those who failed standard dose steroids and splenectomy, requiring further treatment due to unsafe platelets counts (< 30x10⁹), or clinical bleeding [9]. If a patient becomes refractory, new treatment strategies for these patients are needed. Splenectomy continue to provide the highest cure rate (60%-70%) nonetheless, splenectomy is invasive, irreversible associated with
postoperative complications, and its outcome is currently unpredictable leading some physician and patients towards alternative approaches [10].

Rituximab, a chimeric murine-human mouse monoclonal antibody directed against the transmembrane CD20 antigen. This monoclonal IgG-Kappa antibody is used in Non-Hodgkin lymphomas because it induces apoptosis or direct B lymphocyte lysis [11]. In ITP, B cell are responsible of autoantibody production and the subsequent platelets opsonization that allows platelets destruction. Therefore, if B cell clones are eliminated, thrombocytopenia could be reverted. In recent years, rituximab has become a widely used treatment option for chronic ITP. 40% to 60% of chronic ITP patients achieve a partial or complete response following their initial 4 infusion with 375mg/m² of rituximab and only 20% of patients sustains responses lasting at least 3 years. Some patients relapse and require further treatment [12,13,14].

2. METHODS

The study included 41 patients who were registered in hematology department Tripoli medical center with chronic and refractory ITP who were unresponsive to prednisolone including those unsuccessfully splenectomized. Patients had platelet count less than 50x10⁹/L and/or had symptomatic bleeding received rituximab in doses of 375mg/m² infusion over 4 hours. This regimen was indicated weekly for four doses. Responses were classified as complete response CR if platelets > 100x10⁹/L, partial response (PR) if platelets count > 50x10⁹/L and no response (NR) if there were no changes from the baseline platelets count. Each lasting more than 3 months after treatment. Follow up was scheduled monthly for 6 months, and then every 2 months for long term follow up. During follow up, bleeding symptoms, CBC and serum chemistry were ordered for patients. For those patients who responded to rituximab and relapsed, a second course of rituximab was given in same doses. This study was approved by ethical committee of Tripoli medical center.

Statistical analysis

SPSS 17.0 software package (SPSS Inc., Chicago, IL, USA) was used.

3. RESULTS

This study included 41 patients who were diagnosed as chronic idiopathic thrombocytopenic purpura and were received rituximab in their management. 32/41 (78%) were female and 9/41 (22%) were males. Age range between 15-75 years with median age of 39 years and mean of 42 years with SD ± 16. (32/41) 78% of patients presented with symptoms of bleeding, (30/32) 94% had cutaneous bleeding as bruises and Petechial rash, (17/32) 53% had bleeding per gum, (11/32) 34% had epistaxis, (5/32) 15.6% had menorrhagia, (2/32) 6% had hematuria and (1/32) 3% had bleeding per rectum. No patients had a cranial bleeding. No patients had splenomegaly. 7/41 (17%) were diabetic on regular treatment and 9/41 (22%) were hypertensive on regular treatment.

Platelets counts of those patients range from 2-50 x10⁹/L with mean of 25 x10⁹/L, and median of 22x10⁹/L. Mean ESR was 12mm/1st hour. Blood films showed only thrombocytopenia, and bone marrow was compatible with peripheral thrombocytopenia. Viral screen was negative. Steroid as prednisolone 1mg/kg /days was given as first line of treatment. 21/41 (51%) had complete response to steroid and 20/41 (49%) had no response. 14/21 (66.7%) were steroid dependent. 7/21 (33.3%) had a response range from 3 months and 72 months. 10/41 (24.4%) developed steroid complication as diabetes mellitus in 3/10 (30%), and 7/10 (70%) developed hypertension. 4/41 (9.7%) had splenectomy. Rituximab was given as second line as 375mg/m² weekly for 4 weeks. Mean platelets count before rituximab was 26x10⁹/L and median platelets count was 25x10⁹/L. 19/41 (46.5%) had complete response, 5/41 (12%) had partial response of platelets count more than 50x10⁹/L, and 17/41 (41.5%) had no response. Mean platelets count after rituximab treatment 115x10⁹/L. Two patients of responders lost their follow up. Three patients had sustained response less than three months. 19/24 (79%) patients have sustained response beyond the sixth months of follow up. Mean duration of response after rituximab treatment was 27.6 ±21.5 months and median of 24 months with range between 8-96 months. No records of any serious side effect from rituximab. Five had received repeated dose of rituximab. 3/5 (60%) showed complete response and 2/5 (40%) has no response.

4. DISCUSSION

Immune thrombocytopenic purpura in adults is chronic autoimmune disease characterized by antibody mediated thrombocytopenia. Rituximab is a chimeric antibody directed against the CD20 antigen which is a 297-amino acid

phosphoprotein (33-35KD) found on the surface of B cells. CD 20 is highly expressed on the surface of B cells but not on stem cells, Pro-B cells, plasma cells or other cell types. Chimeric antibodies combine the Fab (antigen binding region) of the mouse antibody with the Fc (constant region) of human antibody. These antibodies can bind effectively to target antigens [15]. It is the first monoclonal antibody licensed for treatment of NHL; it has been approved by Food and Drug Administration (FDA) in USA in Nov. 1997. In ITP patients who respond to rituximab have more profound B cell depletion in responders compared with non-responders. Early responders show rapid depletion of anti-platelets antibody compared with delayed fall in late responders [16].

72% of responders have increases in platelets count from 20,000 to 30,000 /µL, complete response was maintained in 28% of patients. Patients who relapsed can respond to second dose with same magnitude and duration as the first response [17]. The dose used is 375 mg/m² once weekly for up to 4 consecutive weeks [18]. Rituximab is the only treatment that is known to induce a lasting response in any substantial percentage of ITP. ITP being a benign immune mediated disease, the patients differ from lymphoma patients not only in the total B cell burden but also in their responses to combination of rituximab and immunosuppressive medication. These observations suggest a role for different factors modulating response to rituximab and underscore the need to explore other immunological phenomenon that may contribute to the pathogenesis of ITP [19]. Rituximab is the only known to induce a lasting response in any substantial percentage of ITP patients. However in one study patients achieving PR with rituximab 11 of 13 patients and approximately one third of patients who achieve complete response tend to have responses lasting less than 6 months [20]. Preliminary results suggest that only 50% sustain their response more than 3 years from initial treatment [21].In one study, investigated response to retreatment with rituximab in chronic ITP patients in previously responder patient, it showed about 30% of patient rituximab induce long lasting responses but even these patients may relapse [22]. In our study, 46.5% had complete response, 12% had partial response and 41.5% had no response. 87.5% has sustain response after sixth months. In Jame Garcia-Chavez et al study includes 18 patients with ITP 28% showed complete response, 28% partial response and 44% had no response. 67% showed sustain response beyond the sixth months of follow up [14]. Rituximab has been given to more than 1 million patients worldwide is generally well tolerated and its short time toxicity is acceptable. In adults with ITP, 40% of patients are complete responders at one year and 20% remain responders at 3-5 years [23,24]. As early relapses may be seen in ITP patients treated with Rituximab and retreatment with this monoclonal antibody offers good results [25]. Aisha Hasan et al study showed that retreatment with standard dose rituximab induce similar responses in 75% of previously responding patients and is well tolerated [22]. 15 of these 20 patients, 75% responded to second course of rituximab (10 CR and 5PR) . Nine of 13 patients who had a CR following retreatment, 2 had a PR, 2 did not respond to retreatment. In our study 5 patients had received repeated doses of rituximab, 3 had CR and 2 had no response. Based on this data rituximab could be a practical treatment option for ITP patients who have relapsed after a response to rituximab [22].

5. CONCLUSION

Rituximab is an effective alternative treatment for chronic ITP with minimal toxicity and side effect and retreatment with standard dose rituximab was successful in patients who had responded to their initial course of rituximab.

REFERENCES

