

Original Research Article

Efficacy and Safety of Rituximab in Pediatric Chronic Immune Thrombocytopenic Purpura in Duhok/Kurdistan

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Abstract

Chronic or refractory Immune thrombocytopenic purpura (ITP) is a difficult-to-manage condition en faced by pediatricians. Known ways of treatment like long term use of steroids and immunosuppressant show poor response and multiple side effects. Splenectomy may be used as a modality. Many studies have been done about effectiveness of rituximab in chronic ITP before splenectomy and its safety. This study was performed to assess the efficacy and safety of rituximab for childhood chronic ITP as a step of treatment prior to splenectomy. A prospective cohort study included 12 patients with chronic ITP in Duhok city. These patients were aged 2 -18 years and had platelet counts $< 20 \times 10^9/L$; for more than 1 year and showed recurrent bleeding from mucous membrane and were treated in different ways with no response. Rituximab was given to them and they were followed up for more than 1 year. Eight patients (66.7 %) attained platelet count of more than $50 \times 10^9/L$ with no signs of bleeding tendency, of them five patients (41.6 %) had complete response (platelet count was $>100 \times 10^9/L$), three patients (25%) had partial response (platelet count was $<50 \times 10^9/L$). Four patients (33.3%) had no response (the platelet count remained low with no raising). No serious side effects were recorded during treatment and follow up.

Key Words: Immune thrombocytopenic purpura, Rituximab, response, Duhok

الخلاصة

ان فرقية نقص الصفيحات الدموية المناعي المزمن من الحالات الصعبة للعلاج التي تواجه اطباء الاطفال والطرق المعروفة للعلاج التي تواجه اطباء الاطفال والطرق المعروفة للعلاج مثل استخدام المدى الطويل للستيرويد وادوية كبت المناعة تظهر ضعف الاستجابة واثار جانبية متعددة . استئصال الطحال يمكن استخدامه كأحد الطرق للعلاج .
دراسات عديدة قد اجريت حول فعالية وسلامة ريتوكسيماب في علاج فرقية نقص الصفيحات الدموية المناعي المزمن قبل عملية استئصال الطحال .
دراسة استباقية شملت 12 مريضا الذين يعانون من فرقية نقص الصفيحات الدموية المناعي المزمن في مدينة دهوك . هؤلاء المرضى تتراوح اعمارهم بين 2-18 سنة . وكان عدد الصفيحات الدموية عندهم اقل من $20 \times 10^9 /$ ليتر لاكثر من سنة وكانوا يعانون من النزف المتكرر من الاغشية المخاطية وقد عولجوا بطرق متعددة مع عدم وجود استجابة . ريتوكسيماب قد اعطيت لهم مع متابعتهم لأكثر من سنة .
ثمانية من المرضى (66.7 %) بلغ عدد الصفيحات الدموية اكثر من $50 \times 10^9 /$ ليتر مع عدم ظهور اية مؤشرات للنزف . خمسة من المرضى (41.6 %) كان لهم استجابة كاملة (عدد الصفيحات الدموية اقل من $50 \times 10^9 /$ ليتر) .
اربعة من المرضى (33.3 %) لم يكن لديهم اية استجابة بقية عدد الصفيحات الدموية منخفضة مع عدم وجود ارتفاع في عدد الصفيحات الدموية .
لم تسجل اية آثار جانبية خطيرة خلال علاج ومتابعة المرضى .

Introduction

Immune thrombocytopenic purpura (ITP) is the presence of thrombocytopenia alone with normal bone marrow and no other cause of thrombocytopenia. It is fall in the number of platelets without toxic exposure or any diseases known to cause a low platelet count.

ITP is primarily a disease of increased peripheral platelet destruction, with most patients having antibodies to specific platelet membrane glycoproteins.

Acute ITP usually happens following an acute infection and mostly resolves within 2 months spontaneously. Chronic ITP is the one that persists for than one year with no specific underlying cause.

The incidence of ITP in children is 50 cases per 1,000,000 per year in USA. New cases of chronic refractory ITP comprise approximately 10 cases per 1,000,000 per year [1,2].

Studies done in Denmark and UK showed the occurrence of childhood ITP as 10-40 cases per 1,000,000 per year. A higher numbers was reported in a study in Kuwait that showed 125 cases per 1,000,000 per year. Peak prevalence occurs in children aged 2-4 years.

Around 30% of children with immune thrombocytopenic purpura (ITP) don't have remission within six months. Chronic ITP is defined as a platelet count that has been $<100 \times 10^9/L$ for longer than 12 months. Refractory ITP now refers to severe ITP that persists after splenectomy. Before splenectomy, patients with ITP are divided into responders and no responders to the different treatment modalities[3,4].

Children with chronic ITP have poor quality of life because of the permanent fear of bleeding, many visits to doctors or admissions to hospital, side effects of medications used or recurrent events of bleeding.

The commonly used treatment for chronic ITP in children are steroids, intravenous immunoglobulin (IVIG), anti-D immune globulin and splenectomy.

Splenectomy is beneficial but it puts young children at a high risk of infection with

encapsulated bacteria. Some chronic ITP cases in children are refractory to all treatment modalities and have persistently low platelets with recurrent bleeding.

Rituximab is a monoclonal antibody that is directed against the CD20 antigen expressed on pre-B and mature B lymphocytes that is approved for use in the treatment of B-cell lymphoma [4,5]. Rituximab rapidly eliminates most circulating B cells with subsequent recovery of B-cell counts 6 to 12 months after therapy. Reducing B cells in the circulation may be effective in the treatment of autoimmune diseases such as ITP. Several studies and case series in adults and children with severe chronic ITP have shown promising results[6,7].

In the last years, it has used as the second line treatment in adults and children with ITP resistant to first line treatment. The review of studies done on adults with ITP showed that rituximab caused overall response (platelet count $>50 \times 10^9/L$) in 62.5% and complete response (platelet count $>150 \times 10^9/L$) in 43.6% of patients. Studies on chronic ITP in children showed a similar effect as adult ITP with variable response rate varied among such studies[8]. Because of many serious acute and chronic complications from splenectomy in pediatric age group specially less than 5 years old, and also difficulty in performing surgery in such patients by many surgeon because of fear of bleeding during operation, make splenectomy unfavorable step. So this study was performed to base rituximab as alternative treatment to splenectomy as curative treatment or to postpone splenectomy to safe age or as late as possible.

Materials and Methods

A prospective study done in Jeen Hematology Center in Duhok, Iraq for three years from February 2012 to February 2015. Ethical approval from Ethics Committee in the Directorate of Health was obtained. The parents of each participant signed a written consent in which they agreed to participate in the study.

Twelve patients with chronic ITP with age at diagnosis (mean age 7.9 years, range 2–

18) 5 male and 7 females were included in this study. Inclusion criteria: Severe, chronic ITP, at least 12 months from diagnosis; platelet counts $<10,000/\text{mm}^3$ twice in past 3 months without bleeding; platelet counts $<20,000/\text{mm}^3$ twice in past 3 months with bleeding. Those patients had been given an average of three treatment modalities for their ITP, including corticosteroids, intravenous immuno-globulin, Anti-D, Azathioprine, Mycophenolate Mofetil. Their platelet counts less than $20 \times 10^9/\text{l}$ with history of frequent petechia, ecchymosis and mucous membrane bleeding with multiple visits to hospital.

Reevaluation of all of them was done regarding CBC morphology, BMA, Anti ds antibody, HIV serology to exclude secondary causes. Patients with secondary causes were excluded.

Rituximab was administered in doses of $375 \text{ mg}/\text{m}^2$ put in 500 ml normal saline solution and infused intravenously over 4 hours. This was given weekly for four doses after prophylactic administration of antipyretic and antihistamines 30 min before rituximab infusion (paracetamol, 10 mg/kg, IV; chlorpheniramine, 0.3 mg/kg, PO; and hydrocortisone, 10 mg/kg, IV). Patients were followed-up 2 weekly for 6 months, then monthly until the end of the study.

Response was described as complete (CR) when the platelet is $>100 \times 10^9/\text{l}$, partial (PR) when platelet $>50 \times 10^9/\text{l}$, minimal response (MR) when platelet $<50 \times 10^9/\text{l}$ and

$>30 \times 10^9/\text{l}$, and no response (NR) when no change in platelet count. Response is sustained (SR) if it is maintained for at least 6 months. The median of platelets count in first six months and second six months was taken for assessing response. History and clinical examination is taken in consideration like petechiae, ecchymosis, and mucous membrane bleeding to assess the response.

Results

Eight of Twelve patients (66.7%) responded to treatment and remained for 6 months after infusion, of them five patients (41.6 %) had CR, three patients (25%) had partial response, and 4 patients (33.3%) had NR at 6 month and remained so after 1 year of infusion as shown in table 2. Of eight patients who responded till 6 month only one of them recurred in second 6 months, while other 7 patients (58.3%) remained so in response till 1 year and still are ongoing in response and showed platelet $> 50 \times 10^9/\text{l}$ for 17 months as a median (a range of 12 to 30 months) after rituximab treatment as in table 1.

No patient discontinued the treatment cycle because of adverse effects of therapy, no any record of side effects like fever, chills, and hypotension during the course of treatment. Only one case of neutropenia, most of them developed lymphopenia in first month of treatment then recovered in subsequent months.

Table 1 :Characteristics of the patients and response

Patient/age/sex (yr.)	Baseline PC ($\times 10^9/l$)	PC median In 1st 6 months ($\times 10^9/l$)	PC median In 2nd 6 month ($\times 10^9/l$)	SR 6 months	Duration of response (months)	Last response Result
1/6/F	10.3	119.5 CR	109.35 CR	Yes	16	CR
2/10/F	15.7	108.0 CR	17.9 NR	Yes	6	NR
3/12/F	19.1	170.0 CR	187.2 CR	Yes	30	CR
4/3/F	12.7	210.4 CR	192.0 CR	Yes	14	CR
5/5/F	9.5	82.0 PR	61.7 PR	Yes	12	PR
6/8/F	14.9	18.2 NR	16.1 NR	No	1	NR
7/8/F	13.5	12.75 NR	9.2 NR	No	0	NR
8/10/M	15.3	161.0 CR	178.0 CR	Yes	20	CR
9/18/M	7.2	18.5 NR	13.6 NR	No	2	NR
10/3/M	7.0	14.3 NR	17.35 NR	No	0	NR
11/8/M	16.5	71.0 PR	87.5 PR	Yes	14	PR
12/2/M	18.7	67.0 PR	36.0 MR	Yes	13	PR
Mean	14.2	87.7	77.158		10.6	

Abbreviations PC platelets counts, SR sustained response, CR complete response, PR partial response, MR minimal response, NR no response, F female, M male.

Table 2 :Response rate

Response Type	Percent of response at 6 month	Percent of response at 1 year
CR	5(41.7 %)	4 (33.3 %)
PR	3 (25%)	2 (16.7 %)
MR	0	1 (8.3 %)
NR	4 (33.3 %)	5 (41.7 %)

Abbreviations PC platelets counts, SR sustained response, CR complete response, PR partial response, MR minimal response, NR no response, F female, M male.

Discussion

There is conflict about the safety and efficacy of rituximab in pediatric chronic ITP by many researchers worldwide.

In a prospective study of 36 severe and/or refractory cases of chronic ITP, the response rate after 4 weekly doses of rituximab was 31% [9]. In the 1-year follow-up study, 8 of the 11 (72%) initial responders maintained a platelet count of $> 150 \times 10^9/L$ without further treatment intervention [10].

Another study of rituximab therapy in severe chronic ITP in children, 63% of patients achieved a stable platelet count ($>150 \times 10^9$) for 4 to 30 months without additional therapy [11].

In this study about 2 third of patients showed response to Rituximab either completely or partial to minimal response. Although it was small number of patient because of limited number of patients with chronic ITP who visited our center, but this study may be based as background for assessment of safety and efficacy of Rituximab in chronic ITP before planning for splenectomy as splenectomy is very difficult decision because of hazards of overwhelming postsplenectomy infection and the risk of hemorrhage during operation. It is preferable this risky procedure avoided or postponed as long as possible, in addition to it not all patients will cure upon splenectomy because of accessory spleen. The American Society of Hematology reported a 72% overall complete remission rate after a splenectomy in 271 children with ITP in 16 case series [12]. The obstacle of using Rituximab in chronic ITP by many pediatricians is the acute and chronic adverse effects of this drug. Bennett et al found during the first 12 weeks of his study, 6 patients (17%) experienced 9 serious adverse events [9].

In the study of Wang et al, three of 24 pediatric patients (12.5%) with chronic ITP developed serum sickness [13]. but in our study no patient developed side effects like fever, chill and this opposite to previous studies and this may prove its safety in children although it require large number of patients to prove its safety. Hematological complications was absent in our study apart from neutropenia in single patient who

recovered spontaneously. Lymphopenia observed in most of our patients in first month of treatment but it return normal later on. There were no other illnesses in this group of patients. Rituximab is safe and efficient step of treatment for pediatric chronic ITP who are refractory to other standard agents, before splenectomy and it is wise to be applied in such patients [14,15,16]. The toxicity profile of rituximab is absent in the majority of patients. Given the favorable safety profile and results from other studies, rituximab may be preferable to splenectomy particularly in younger patients who are at relatively higher risk of infection with encapsulated organisms. However the long term effects and safety have not been established [17].

Randomized controlled trials to define the role of rituximab in treating pediatric ITP are greatly needed [18].

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