ORIGINAL ARTICLE

Two Years Effectiveness of Rituximab in Refractory Idiopathic Thrombocytopenic Purpura

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ABSTRACT

Background and aim: The treatment of immune thrombocytopenia (ITP) started with steroids but most patients will relapse or have significant adverse effects. The use of Rituximab was greeted enthusiastically: it led to up to 60% response rates, making it the main alternative to splenectomy, with far fewer side effects. The aim of study to assess the 2 years effectiveness of rituximab in the managements of patients with chronic and refractory immune thrombocytopenic purpura (ITP).

Methods and Materials: Retrospective study included 22 patients labeled as refractory chronic idiopathic thrombocytopenic purpura (ITP), This study was conducted at King Hussein Medical center / Amman - Jordan, Hematology and Oncology Department between February 2017 and February 2019, a weekly 4 doses of Rituximab 375mg/m2 were given, a 2 years regular follow up on the efficacy and safety of rituximab were identified.

Results: The mean age at diagnosis was 36.7 years (19-54), Mean platelet count before rituximab treatment was 8×109 /L.All patients were followed for 2 years , the overall response rate to rituximab was 59.1 % at 6 months (CR 31.8 %, PR 27.2 %) ,The median time to response was 4 weeks (1-8 wks.) ,with 45.5 %of all patient responded within 1 month, 22.8% lost response at 1 year (accumulative 1 year response 36.3%) , further 9.1% lost response at 2 years (accumulative 2 year response 27.2 %) , 13.6% did not showed any response.

Conclusion: over 2 year's observation, our study confirms effectiveness and safety of rituximab in management of chronic refractory ITP.

Key words: Chronic refractory ITP, Anti-CD20, Rituximab.

INTRODUCTION:

Chronic immune thrombocytopenia (ITP) is an autoimmune disease, characterized by production of antibodies of IgG subtype against platelets which results in early destruction and low platelets count of with variable clinical presentation ranging from no symptoms to bruising to severe bleeding.[1] It persists longer than 6 months without detected underlying cause.[2] The aim of the treatment is not to normalize platelets count but to prevent bleeding.[3]. Initial treatment is typically corticosteroid , infusional methylprednisolone or dexamethasone , hospitalization is usually recommended for active bleeding or lower platelets count less than 20×109 /L , while oral prednisolone (1.0 to 1.5 mg/kg/day) may sufficient in milder cases.[4] Most patients will relapse or have significant adverse effects after prolonged use of high dose of corticosteroid ,that necessitate other treatment.[5] Many pharmaceutics have been tried in this issue they include , IVIG ,Azathioprine, Mycophenolic acid , Danazol, chemotherapy gents, Dapson and splenectomy.[6] About 30 % of adults with ITP fail to respond to conventional treatment developing what is called refractory disease requiring further treatment to keep platelets to safe level.[7] In ITP B lymphocyte play major rule in secreting antibodies that lead to destruction of platelets; therefore, B cells depletion is considered rational for treatment of ITP.[8] Rituximab, a monoclonal antibody directed against CD20, a membrane glycoprotein expressed on the surface of B cells, was introduced for the treatment of B cell lymphomas towards the end of the 1980s.[9] Binding to an antigen that is only expressed on mature B cells, Rituximab leads to a fast and deep, but reversible B-cell depletion.[10] This mechanism and the low toxicity profile represented the rationale for its use in the treatment of autoimmune conditions, especially those in which B-cell activity was considered the main pathogenic mechanism, such as ITP. Many studies have been carried out in this field: in monotherapy with different dose

schedules and in combination with other drugs, proving its efficacy, with some differences between these studies.[11]. The aim of study to assess the 2 years effectiveness of rituximab in the managements of patients with chronic and refractory IITP.

MATERIALS AND METHODS

Twenty two patients, 12 females and 10 males, older than 18 years of age, were diagnosed with chronic refractory ITP, retrospectively followed after 2 years of treatment with Rituximab for refractory ITP between February 2017 to February 2019. The study was conducted at Department of Hematology and Oncology , at King Hussein Medical center / Amman -Jordan. Rituximab 375mg/m2 diluted in 500 cc normal saline and infused intravenously over 4 hours weekly for 4 doses 10, a premedication 11 with Antihistamines, antipyretic and corticosteroid were commonly used to Prevent infusion reaction. Outpatient follow up was with weekly ou patient clinic visit in the first month, fortnightly in the 2nd month , monthly from 3rd to 6th months , then 2 monthly till 2 years. Platelet count were recorded at base line and after 1st,2nd,3rd ,4th ,6th,8th,12th, 16th , 20th, 24th, 36th, 52th ,78th , and 104th weeks. The response to Rituximab was identified as complete (CR) when platelet count reached ≥ 100 × 109 /L , partial (PR) when achieved ≥ 50 -99× 109 /L ,those who had platelet count 30-49× 109 were considered to have minimal response (MR) , and no response (NR) when platelet count less than 30 × 109. We defined early response (ER) if response was achieved within 6 weeks of rituximab infusion, late response (LR) when occurring after 6 weeks, the overall response (OR) was the summation of both (CR) and (PR) with exclusion of (MR), sustained response (SR) as it was maintained at least 6 months 14+15. And duration of response (DOR) as a time between (CR) or (PR) to loss of response (platelet count ‹30 × 109 /L). In our review we collected data to include: age, gender, duration of ITP before Rituximab, previous therapies, and platelet count prior to and at fixed weeks post Rituximab infusion. The study was approved by the Ethics Committee of The Royal Medical services.There is no conflict of interest to show and this study had no fund from any pharmaceutical companies.

RESULTS

Our study included a 22 patients who were diagnosed with chronic refractory ITP, treated with rituximab 375 mg/m^2 weekly for four doses. Patient characteristics are shown Table 1, serial platelet count at fixed weeks of follow up during the 2 years, type of response and time to response are shown in Table 2. The mean age was 36.7 years (range ,19-54) , female: male ratio was 12:10 ,mean platelet count was 8 × 109 / L (range , 2-16× 109 / L) , all patients completed 2 years follow up , mean number of agents had been received before Rituximab was 4.5 (range, 4-6), 3 (13.6 %) patients had been splenectomized. The median duration of ITP before treatment with rituximab was 13 months..

Table 1: Patient characteristics

No./Parameter	Age(Yrs)	Sex	Age	Duration of ITP before Rx (months)	Number of previous therapies
1	19	F	19	12	5 P,AZ,MP,V,IV Ig
2	23	M	23	10	5 P,AZ,D,MP,V
3	52	M	52	24	5 P,AZ,D,MP,IV Ig,S
4	47	F	47	16	6 P,AZ,D,MP,V,IV Ig
5	54	F	54	8	4 P,AZ,INF,MP
6	22	F	22	6	4 P,AZ,INF,V
7	52	M	52	10	6 P,AZ,D,MP,V,IV Ig
8	30	F	52	9	4 P,AZ,MP,IFN
9	34	M	30	12	4 P,AZ,D,MP,V
10	41	F	34	9	4 P,AZ,MP,IFN
11	43	M	41	8	5 P,AZ,D,MP,IFN
12	39	M	43	10	5 P,AZ,INF,MP,S
13	30	M	39	12	4 P,AZ,D,MP
14	28	F	30	16	4 P,AZ,D,MP,V
15	24	F	28	10	4 P,AZ,MP,IFN
16	27	M	24	7	4 P,AZ,D,MP
17	53	F	27	9	4 P,AZ,MP,S
18	47	F	53	12	4 P,AZ,IFN,MP
19	42	F	47	8	4 P,AZ,MP,V
20	22	M	42	13	6 P,AZ,D,MP,V,IV Ig
21	24	F	22	7	4 P,AZ,MP,IFN
22	26	M	26	16	4 P,AZ,INF,MP

P; prednisone, Az ; azathioprine, MP; Mycophenolic acid, V ;vincristine, IV Ig ;intravenous Immunoglobulin ,D ;danazol , S; splenectomy ,IFN; interferon alpha 2b.

Table 2: Type of response and time to response

No./ Parameter	PC before Treatment	PC 1 week post treatment	2 wks	3 wks	4 wks	6 wks	2 mnth	3 mnth	4 mnths	5 mnths	6 mnths	1 yr	2 yrs	2 yrs type of response	Time to Response (wk)
1	4	17	22	18	13	21	22	27	19	22	28	29	23	NR	NR
2	6	165	177	182	163	133	149	277	189	233	323	186	111	CR	1
3	13	33	47	117	159	139	142	133	168	119	122	154	122	CR	1
4	3	22	19	33	44	43	69	71	53	57	52	28	21	NR	3
5	11	22	27	27	23	28	19	21	22	27	23	20	21	NR	NR
6	8	28	92	101	87	91	81	72	69	81	108	101	59	PR	2
7	2	13	17	22	19	22	23	18	27	28	17	25	28	NR	NR
8	6	14	18	25	9	17	13	13	26	22	14	19	10	NR	NR
9	4	17	19	22	37	44	72	55	62	69	67	42	24	NR	4
10	6	29	36	42	69	65	71	69	91	76	109	58	44	MR	2
11	9	53	61	73	58	71	62	59	66	71	67	53	55	PR	1
12	12	31	45	135	155	132	142	121	159	179	268	117	107	CR	1
13	2	19	37	22	31	28	29	28	23	26	29	27	27	NR	2
14	13	17	16	22	19	26	25	27	31	37	41	27	28	NR	16
15	6	16	23	29	51	55	67	53	58	66	69	25	29	NR	4
16	14	14	17	22	26	27	22	19	29	26	21	29	25	NR	NR
17	2	25	17	31	40	59	65	69	75	82	91	47	33	MR	3
18	13	16	19	33	23	33	31	27	29	33	27	29	22	NR	NR
19	9	33	41	47	132	143	155	163	181	244	175	126	117	CR	1
20	5	12	32	51	57	59	53	52	53	55	50	29	29	NR	2
21	12	18	23	29	61	57	77	71	89	99	100	55	28	NR	4
22	16	22	28	33	42	39	41	37	28	29	33	22	24	NR	3

At 6 months OR was achieved in 13 patients (59.1 %) : 7 patients obtained CR (31.8%) , and 6 achieved PR (27.2%), 9 patients (40.1 %) were considered treatment failure (2 of them reached minimal response (MR)). At 1 year OR was achieved in 8 patients (36.3 %) , of them 5 patients kept their CR (22.7%) , and 3 achieved PR (13.6%). This means 2 patients whom achieved CR at 6 months changed to PR at 1 year, and 5 patients achieved PR became treatment failure. At 2 years OR was achieved in 6 patients (27.2 %) , of them 4 patients kept their CR (18.2%) , and 2 achieved PR (9%). One patient who achieved CR at 1 year changed to PR, and two who obtained PR at 1 year became treatment failure at 2 years. Median time from Rituximab treatment to achieve at least PR in responders was 3.9 weeks (27.5 days).8 of the 13 responders (61.5 %)1 showed SR for at least 6 months

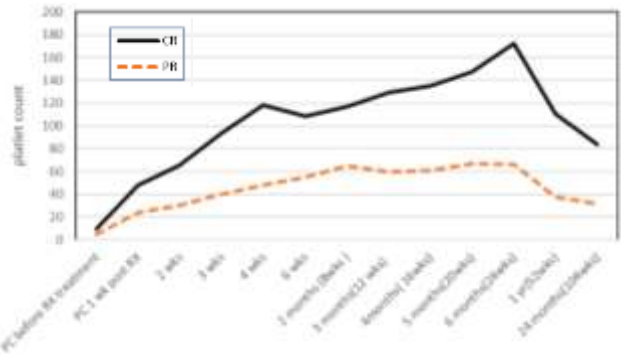

Figure 1: Serial median platelet count during 2 years follow up in the two response type (CR and PR)

We did not find relation between pretreatment duration and response type. PRs tended to relapse more often and earlier than CRs, even after a 1-year duration of response. After Rituximab treatment with responses lasting at end of study (2 years) the relapse rate in CR responders was 42% (3of 7) while it was more in PR 71% (5 of 7) (P< 0.001). Figure 1 shows serial median platelet count during 2 years follow up in the two response type (CR and PR).

DISCUSSION

Because chronic refractory ITP patients do not respond to multi lines of treatment, they survive with low platelet count , a situation which carries a variable clinical risk ranging from No symptoms to bruising to severe life threatening bleeding (12). That necessitates many hospitalization and treatment adherence which will compromise life style (13).Rituximab is considered one of the treatment choices that induce a durable response , it has an initial curative response in 50-60 % of chronic refractory ITP patients ,and considerable sustained response.[12,13,14] The aim of our study was to assess the efficacy of Rituximab obtained in 22 chronic refractory ITP patients who had persistent very low platelet count and received a mean of 4.5 therapies prior to use of Ritximab. We noticed 13 favorable initial responses (59.1%) , 7 (31.8 %) patients had CR , and 6 (27.2%) had PR , different criteria of response were defined by various studies , our findings are comparable to several other studies.[15,16,17,18,19].Based on 2 years follow up of our patients ,we confirm 23 that response rate achieved by Rituximab (59.1%) after failure of many therapies was quite satisfactory ,providing that Rituximab was well tolerated with minor resolvable adverse effect by using premed as paracetamol and antihistaminic ,

most of the patients (61.5%) had SR; and platelet favorable count response was immediate (3.76 weeks) , 45.5 % of all 22 patients responded within 1 month which agree with previous reports(20,21,22,23). We did not find relation between pretreatment variables like: age, gender, number of pre Rituximab treatments , previous use of specific drug , pre Rituximab ITP period , base line and pre rituximab platelet count , this fact was noticed in systemic review [24]. As previously suggested by systemic review pre Rituximab splenectomy is not significant predictor of the response to Rituximab.[25,26,27] We could not assess this particular variable in our study because just 13.6% of our patient had been spleenectomised as compared to 50.5% in the systemic review.[19,24,25].Actually we did not evaluate other possible variables that may affect the response to Rituximab like B cell count and platelets antibodies.[27]. We noticed two pattern of response to rituximab in responding patient : Early (ER) 84.6 %[28,29] achieved platelet count ≥ 50 × 109 within 6 weeks (all CR patient 7/7 and 4 of PR patient 4/6) , and late (LR)15.4% beyond 6 wks (the other 2 of PR 2/6) ,we noticed that CR responder are achieving earlier response than PR responders a notice that disagrees with previous reports.[29,30,31] We did not noticed any delay response in the non-responding patients. At 6 months follow up OR was achieved in 13 patients (59.1 %) , of them 7 patients obtained CR (31.8%) , and 6 achieved PR (27.2%), 9 patients (40.1 %) were considered treatment failure (2 of them reached minimal response ‹30 × 109 /L). At 1 year 5 of the 7 patients who achieved CR at 6 months kept their CR , the other 2 became PR ,but of the 6 who obtained PR at 6 months just 1 kept PR at 1 year, the other 5 became treatment failure ,this resulted in 1 year overall response rate of 8/22 (36.3 %) this was parallel to some meta analysis.[35,36] Even there was a large variation in the individual studies regarding the reported 1 year overall response rates (33−85% at 1 year after Rituximab treatment). At 2 years OR was achieved in 6 patients (27.2 %) , 4 patients kept their CR (18.2%) , and 2 achieved PR (9%). One patient who kept 1 year CR changed to PR, and two patients who obtained 1 year PR became treatment failure. there were a large variations regarding long term efficacy of rituximab in chronic refractory ITP ,: Khellaf et al found that the overall 2 years response was 39% (33). In other studies a 2 years overall response rate was observed in about 40%.[36,38,39].The explanation of the lower result attained in our study at 2 years is that we did not consider Minimal response (MR) as favorable as the other studies. As for toxicity profile of Rituximab ,Infusions related adverse reactions were the most frequent event , in most times it was controlled by using premedication 11 with Antihistamines, antipyretic and corticosteroid , Rituximab was quitted only once because of dyspnea , laryngeal discomfort and hypotension that necessitated in hospital observation, the patient was discharged the day next and excluded from the study , other side effects were tolerable and easily manageable , these included chills, low grade fever , skin rash , palpitations, and paresthesia. We did not noticed sever infections, nor progressive multifocal leukoencephalopathy (PML).

Limitations

1 st ,The follow up duration was limited to 2 years so no long term data of response are available , 2 nd our study was small as many other relative studies which are still relatively small , 3rd we have to consider the financial issue of Rituximab according to local resources because Rituximab is relatively is expensive 4 th Eltrombopag which is encouraging in ITP patient was not elucidated in comparison to Rituximab , new studies showed a promising benefit of this therapy and could be potential alternative of Rituximab.

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