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ORIGINAL ARTICLE

Clinical Efficacy and Safety of High-Dose Dexamethasone Plus Low-Dose Rituximab as First-Line Therapy in Newly Diagnosed Primary Immune Thrombocytopenia

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Abstract Standard-dose prednisone as first-line therapy for primary immune thrombocytopenia (ITP) can not obtain high long-term responses. Results from high-dose dexamethasone course administered in adult newly diagnosed ITP were promising. The role of standard-dose rituximab in first-line treatment of newly diagnosed ITP were also investigated. We retrospectively analyzed the efficacy and safety of high-dose dexamethasone plus low-dose (100 mg/w) rituximab for treatment of adults newly diagnosed ITP. A total of eighteen patients received dexamethasone 40 mg/day for 4 consecutive days (days + 1 to + 4), rituximab 100 mg once weekly for a total of 4 weeks (days + 7, + 14, + 21 and + 28). Non-responders accepted the repeated dexamethasone treatment every 2 weeks for a total of up to 3 treatment cycles. The overall response was 100% at 28th day. Median follow-up was 17 months (1–33 months). Six patients (33.3%) relapsed. Sustained complete response or response after 6 months and 12 months of follow-up were reached in 83.3% (15/18) and 61.5% (8/13) of patients respectively. The 12-month and 15-month cumulative relapse-free survival were 69.3% and 60.7%. Incidence of adverse effects was 11.1% (2/18). High-dose dexamethasone plus low-dose rituximab therapy had high efficacy and well tolerability as first-line treatment option in newly diagnosed ITP.

Keywords Immune thrombocytopenia · Newly diagnosed · Rituximab · Dexamethasone

Introduction

Primary immune thrombocytopenia (ITP) is an autoimmune disease characterised by peripheral platelet count below 100×10^9/L and possible hemorrhagic complications, due to premature platelet destruction by self-reacting antibodies in addition to an impairment of platelet production [1]. Bleeding symptoms of ITP, involving skin, visible mucosae, and organs, range widely [2]. The patients are probably asymptomatic with blood platelet account $> 50 \times 10^9$/L, spontaneous bleeding may develop with the decrease of platelet counts [3].

The low morbidity and mortality in patients with moderate thrombocytopenia, at the same time, equal contribution to death from bleeding and infection, support clinical practice refraining from further treatment [4]. Corticosteroids, intravenous immunoglobulin (IVIg) and anti-D immunoglobulin (anti-D), are first-line treatments recommended by guidelines [5, 6]. A general standard prednisone therapy, 1 mg/kg/day for 3–4 weeks and tapering, can raise platelet counts rapidly in around 75% of patients, but, long-term responses are seen in only 25% of patients [7]. At least half of the initial patients will relapse and may suffer from the adverse effects of further treatment. Among the refractory chronic ITP patients, who did not respond to splenectomy, about 17.6% were extremely resistant to therapy and who have a significantly higher mortality rate from ITP and its treatment than ITP patients who do not

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require or who respond to surgery [8]. So increasing the response rate of first-line treatment and duration of response is of great significance.

Short course of high-dose dexamethasone (40 mg/day for four consecutive days) was proved to be a effective initial therapy for adults with ITP [9]. The initial response rate was 85% and 42% had sustained response rate after just one four-day course of high-dose dexamethasone therapy. Moreover the therapy was well tolerated and had fewer side effects than that in patients who received conventional doses of prednisone for longer periods.

Rituximab is a chimeric monoclonal antibody specifically recognizing the CD20 phosphoprotein expressed on the surface of normal B lymphocytes and B-cell lymphoma [10]. It can cause a marked, transient, B-cell depletion and this effect has been exploited for the salvage treatment of chronic and refractory ITP (weekly infusion of 375 mg/m^2 for 4 consecutive weeks [11–16]. A reduced dosage of rituximab (weekly infusion of 100 mg for 4 consecutive weeks) were reported to be active in ITP, though the kinetic of response were significantly different from that of standard dose [17].

Prospective studies have investigated the role of standard-dose rituximab plus high-dose dexamethasone in first line treatment of newly diagnosed ITP [18, 19]. To date, few study has evaluated the efficacy of high-dose dexamethasone plus low-dose rituximab in newly diagnosed ITP. We report the results of the retrospective study including eighteen adult, newly diagnosed ITP patients.

Patients and Methods

Patients

A total of 18 patients with primary newly diagnosed ITP, accepting low-dose rituximab in combination with high-dose dexamethasone from January 2013 to September 2015 in Department of Hematology, affiliated cancer hospital of Zhengzhou university, were retrospectively reviewed. We adhered to the criteria of the International Working Group (IWG) and the American Society of Hematology (ASH) practice guideline for ITP diagnosis [6, 20]. Secondary ITP patients such as those with systemic lupus erythematosus, human immunodeficiency virus infection, Helicobacter pylori infection, and drug exposure, were strictly excluded, and all ITP patients did not use the relevant treatment before treatment. The program was approved by the hospital ethics committee and the patient signed an informed consent form prior to the infusion. The study was in accordance with the Declaration of Helsinki and was approved by Institutional Review Board of Chinese Zhengzhou university.

Treatment

Rituximab was administered in a fixed dosage of 100 mg intravenous infusion once weekly for a total of 4 weeks (days + 7, + 14, + 21 and + 28). Each time intravenous administration of rituximab and 100 ml saline continuous micro pump pumping, the initial infusion rate is 50 mg/h, after the first 60 min, can increase 50 mg/h every 30 min, maintain infusion for 2 h. Dexamethasone was also intravenously infused in a dosage of 40 mg once daily for 4 consecutive days (days + 1 to + 4). Non-responders accepted the repeated dexamethasone treatment every 2 weeks for a total of up to 3 treatment cycles [21]. Other additional steroid, intravenous immunoglobulin and immunosuppressive drugs was not administrated.

Response and Toxicity Criteria

According to the recommendation of the IWG [20], the criteria for treatment responses were defined as follows: (1) complete response (CR) was defined as a platelet count $\geq 100 \times 10^9$/L and absence of bleeding; (2) response (R) was defined as a platelet count ≥ 30 but $< 100 \times 10^9$/L and at least twofold increase the baseline count and absence of bleeding; (3) no response was defined as a platelet count $< 30 \times 10^9$/L or a less than a twofold increase of baseline platelet count or bleeding. The overall response rate (OR) included R and CR. Relapse was defined as the loss of CR/R after achievement of CR/R. Relapse-free survival (RFS) included the whole period of spontaneous maintenance of the best response achieved (CR or R). Platelet counts were measured every 3 days during treatment period, weekly during the first 2 months after treatment and then monthly. Adverse events were assessed according to Common Terminology Criteria for Adverse Events (version 4.0).

Statistical Analysis

The probability of RFS was calculated using the Kaplan–Meier method. The logistic regression was used to assess whether response to treatment was associated with age, gender, baseline platelet count and time to response. Analyses were considered statistically significant when P values were less than or equal to 0.05. Statistical analysis was carried out using SPSS software version 19.0

Results

Patients

We retrospectively reviewed 18 adult patients ($\geq$ 18 years, 3 males and 15 females) with newly diagnosed ITP

accepted high-dose dexamethasone plus low-dose rituximab as first-line therapy. The median age was 26 years (range 18–62 years). The median platelet count at diagnosis was 10.5 × 10^9/L (1–26 × 10^9/L). All the patients displayed bleeding symptoms at diagnosis, which included petechiae (grade 1, n = 8; grade 2, n = 2), ecchymoses (grade 1, n = 4), Epistaxis (grade 3, n = 1), gum bleeding (grade 1, n = 1), and menorrhagia (grade 2, n = 2). The main clinical and laboratory baseline characteristics were summarized in Table 1.

Efficacy

All eighteen patients completed the therapy with a compliance of 100%. Fifteen patients (83.3%) received one course dexamethasone, two patients (11.1%) received two courses and only one patients (5.6%) received three. Median time to response was 7.5 (3–23) days (Table 2). Median time to complete response was 10 (6–35) days. At 28th day of the therapy, OR, CR and R rates were 100%, 61.1% (11 of 18) and 38.9% (7 of 18), respectively. Univariate logistic regression showed no association of CR with age, $P = 0.095$ (OR = 0.913, 95% confidence interval [CI]: 0.821–1.016), gender, $P = 0.733$ (OR = 0.507, 95% CI 0.010–25.363), baseline platelet count, $P = 0.156$ (OR = 0.811, 95% CI 0.607–1.083), or time to response, $P = 0.648$ (OR = 1.087, 95% CI 0.795–1.558). Characteristics of each patient at baseline and after treatment are showed in Table 3.

Median follow-up was 17 months (1–33 months). A total of 6 patients (33.3%) relapsed, 2 of 11 CR (18.2%) and 4 of 7 R (57.1%) respectively. Sustained CR or R after 6 months of follow-up was reached in 83.3% (15/18) of all patients. At 12 months follow-up, sustained R or CR was achieved in 61.5% (8/13) of patients. Stepwise Cox regression model showed that RFS was not associated with age ($P = 0.133$), gender ($P = 0.339$), baseline platelet count ($P = 0.333$), time to response ($P = 0.185$) or reach CR or not ($P = 0.166$). Five patients need further treatment, one accepted splenectomy, two accepted oral danazol plus prednisone, another two accepted amifostine.

Table 1 Baseline characteristics

Age, median (interquartile range, IQR)	26 (20–46)
Sex, females, n (%)	15 (83.3%)
Baseline platelet count × 10^9/L, median (IQR)	10.5 (7–18)
Dexamethasone cycles during treatment	
1 cycle, no. of patients (%)	15 (83.3%)
2 cycles, no. of patients (%)	2 (11.1%)
3 cycles, no. of patients (%)	1 (5.6%)

Table 2 Response rate and outcome after treatment

Patients	18
CR	12 (66.7%)
R	6 (33.3%)
Median time to response, days (IQR)	7.5 (5–10)
Median time to CR, days (IQR)	10 (7–13.5)
Median time of follow-up, months (IQR)	17 (9–21)
Relapse rate	6/18 (33.3%)
Post CR relapse	2/11 (18.2%)
Post R relapse	4/7 (57.1%)

On the Kaplan–Meier curve (Fig. 1), mean time without relapse was 20.1 months [95% CI 14.5–25.8]. The 12-month and 15-month cumulative RFS were 69.3% and 60.7%.

Safety

This therapy was well tolerated. One patient, at the 25th day of the therapy, developed an severe pneumonia, which was at one time refractory to antibiotic therapy and antifungal agents. Another patients, at the 22nd day of the therapy, developed cerebral thrombosis after complete response to treatment and had well recovery after neurologic therapy. No other infectious, hematologic or extrahematologic complications were documented during follow-up.

Adverse Reactions

Adverse reactions observed during the treatment of rituximab are common. Mostly caused by infusion-related or cytokine release, such as fever, chills, dizziness, headache, weakness, nausea, vomiting, high blood pressure, sinus tachycardia, itching, urticaria, throat tightness, short-term hypotension, etc. But all patients had no adverse reactions in the infusion in our treatment plan.

Discussion

The goal for ITP initial treatment is to provide a safe platelet count preventing major bleeding and obtain sustained response. Results from a multicenter pilot study planned by GIMEMA (the Gruppo Italiano Malattie EMato-logiche dell'Adulto) ITP Working Party was promising, in which pulsed high-dose dexamethasone was given as first-line treatment in 4-day pulses every 14 days, for 4 cycles [21]. The overall response rate was 85.6%, with significant difference between the second and third

Table 3 Characteristics of each patient at baseline and after treatment

Patient	Age	Sex	Plt count $\times 10^9$/L before treatment	Time to initial response (day)	Plt count $\times 10^9$/L at 14th day	Plt count $\times 10^9$/L at 28th day	Response at 28th day	Time of follow up (month)	Time of relapse (day)
1	62	F	7	7	536	412	CR	17	71
2	41	F	9	6	103	129	CR	29	
3	26	F	16	3	198	250	CR	20	
4	18	M	25	23	25	98	R	17	
5	60	F	26	11	51	86	R	21	221
6	46	F	22	10	58	56	R	19	56
7	26	F	19	4	97	78	R	21	85
8	24	F	3	10	107	115	CR	17	
9	18	F	18	8	149	325	CR	15	
10	21	F	8	3	259	249	CR	16	
11	23	M	11	6	187	127	CR	33	402
12	39	F	8	8	136	201	CR	9	
13	22	F	2	5	278	315	CR	28	
14	19	F	14	9	92	87	R	7	
15	47	M	7	11	28	83	R	9	
16	26	F	1	4	252	234	CR	3	
17	18	F	14	6	175	171	CR	1	
18	53	F	10	10	47	81	R	12	286

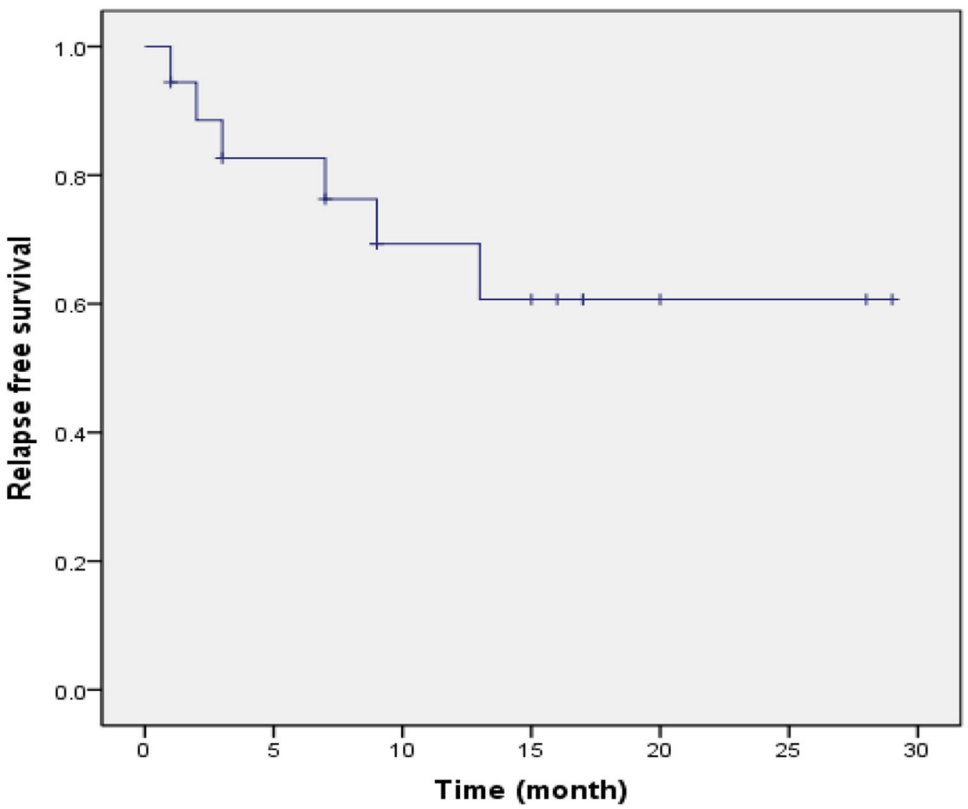

Fig. 1 Kaplan–Meier curves of relapse-free survival after treatment

cycle (75.8% vs. 89%, $P = 0.018$). RFS at 15 months was 81% and long-term responses was 74.4%, lasting for a median time of 8 months (range 4–24 months). Excluding 44 patients younger than 18 years old in the study, persistent response rate was 66.7% (32/48 evaluable adult patients) without any therapy.

Gudbrandsdottir et al. [19] reported higher response rates and longer time-to-relapse with dexamethasone and rituximab (standard dose) versus dexamethasone in patients with newly diagnosed ITP. An increased incidence of grade 3–4 adverse events in the rituximab + dexamethasone group were also observed ($P = 0.04$). Zaja et al. [18] also reported that up-front addition of rituximab (standard dose) to dexamethasone in treatment of newly diagnosed ITP improved outcomes and yielded longer sustained response rates than dexamethasone alone. From the above [9, 18, 19, 21], High-dose dexamethasone has a rapid effect on ITP patients, and its effect is fast. The effect of CD4 + CD25+ regulatory T lymphocytes in peripheral blood is significantly greater than that of conventional doses of dexamethasone.

Some experimental studies [22–24] have shown that low-dose rituximab treatment of refractory ITP also shows similar efficacy to standard dose of rituximab in the treatment of ITP, and its adverse reaction rate is lower, and the treatment price is lower than the standard dose. Our findings suggest that the addition of low-dose rituximab to high-dose dexamethasone in treatment of newly diagnosed ITP induced high response rates and sustained response rates. To our knowledge, till now, only Gomez-Almaguer et al. [25] have reported the same regimen as front-line therapy in newly diagnosed ITP adults. The initial responses in our study were really satisfactory, especially the OR rate of 100% (61.1% CR and 38.9% R) at 28th day which was higher than that in Gomez-Almaguer's study (OR rate 90.5%). One patient, achieved CR until the 35th day, finally elevated the OR rate to 66.7%. Sustained CR or R after 6 and 12 months follow-up were 83.3% and 61.5%, respectively. Gomez-Almaguer reported the relapsed rate and 12-month cumulative RFS were 15.8% and 84%, which was better than that of our study (33.3% and 69.3%). Both Gomez-Almaguer's and our study showed a high response rate and low relapse rate, confirming the high efficacy of adding low-dose rituximab to high-dose dexamethasone as first-line therapy.

Recently, a systematic review and meta-analysis of randomised controlled trials analyzed 463 patients who had not undergone splenectomy at the time of enrolment [26]. Patients who received rituximab plus standard of care were more likely to achieve a complete response sustained by the end of 6 months than were patients treated with standard of care alone (weighted proportions: 46.8% vs. 32.5%; RR 1.42, 95% CI 1.13–1.77, $P = 0•0020$). Rituximab was not associated with a reduction in bleeding or an increase in infections. A multicentre, randomised, double-blind, placebo-controlled trial, rituximab as second-line treatment for adult immune thrombocytopenia (4 weekly infusions of 375 mg/m^2 rituximab or placebo), showed no reduction in the rate of long-term treatment failure with rituximab within 78 weeks, but an apparently longer duration of response and numerically higher response rates [27]. Median time to relapse in patients who achieved overall response was 36 weeks in the rituximab group and 7 weeks in the placebo group ($P = 0.014$) and in patients who achieved complete response, the median times to relapse were 76 weeks and 49 weeks, respectively ($P = 0.19$). It seems that the efficacy of rituximab as a splenectomy-sparing treatment becomes known gradually, but as front-line treatment, especially low-dose, is still to be proved. Treatment with pulsed high-dose dexamethasone was well tolerated [21]. Though rituximab can induce persistent hypogammaglobulinaemia, it has not been associated with an increased risk of infections [26–28]. Adding standard dose rituximab to dexamethasone as front-line therapy made increased incidence of grade 3–4 adverse events, but incidences of serious adverse events were similar to dexamethasone monotherapy [18, 19]. The adverse events in the present study is about 11.1% (2/18). All the patients showed good tolerance to the therapy. Few patient had fever or thrill during rituximab infusion.

The main limitation of this study is its retrospective design with possible bias and the number of patients was low. Randomised controlled trials are needed for further assessment of the efficacy and safety of this regimen.

In conclusion, our study suggests that the therapy of high-dose dexamethasone plus low-dose rituximab was well tolerated and eutherapeutic for newly diagnosed ITP patients. Prospective clinical trials are necessary to further evaluate the role of this therapy in the therapeutic strategy in newly diagnosed ITP patients.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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