A second-line escalating treatment strategy for children with severe chronic immune thrombocytopenia: A retrospective data from a single-center

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Declarations

Ethical approval: This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (IRB) of Beijing Children's Hospital, Capital Medical University. All parents signed informed consent forms.

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【Abstract】

Background: Childhood immune thrombocytopenia (ITP) is a disease that usually runs a benign, self-limiting course. First-line treatments are usually sufficient for those in need of management, yet approximately 20% of those patients do not respond well to first-line therapy and consequently develop chronic ITP.

Objective: To analyze the effect of a novel second-line escalating treatment strategy (high-dose dexamethasone (HDD), low-dose rituximab to eltrombopag) for children with severe chronic immune thrombocytopenia (SCITP).

Materials and Methods: This study was a single-center, retrospective cohort study. The data of children SCITP who received escalating treatment strategies in our center were collected between June 2017 and August 2019. The second-line escalating strategy included 3 steps: Step I (6 courses high-dose dexamethasone: HDD), Step II (HDD combined with low-dose rituximab), and Step III (eltrombopag).

Results: A total of 30 cases (18 males and 12 females) were included; the median age was 8.83 (1.42-13.9) year-old, the duration time of ITP was 20.5 (12.0-96.0) months, and the platelet counts were 15 (3-29) $\times 10^9$/L. After the median 14 (12-37) months' treatment, the remission rate was 36.7% (11/30), and the sustained response (SR) rate was 68.2% (15/22). The distribution (remission rates) from step I to III were: 30.0%, 9/30 (33.3%, 3/9); 13.3%, 4/30 (50%, 2/4); 56.7%, 17/30 (29.4%, 5/17), respectively. In eltrombopag (step III) cases, 47.5% (8/17) maintained platelet $\geq 50\times 10^9$/L, 37.5% (3/8) dose tapering, and 25% (2/8) were successfully discontinued from medication. The number of patients at 12^{th}, $24^{th,}$ and 36^{th} months was 30, 7, and 2, with the total response (TR) and remission rates of 80% (36.7%), 57.1% (28.6%), and 50% (50%), respectively. The total relapse rate was 26.7% (8/30) ， three cases(75%, 3/4)from Step II and 5 cases (41.7% ,5/12)from Step III, none in Step I.

Conclusion: The new second-line escalating strategy for children SCITP has an effective improving rate with 36.7% remission and 68.2% SR; 30% could benefit and retain stable response from HDD treatment. Combined treatment with eltrombopag can reduce the relapse rate of low-dose rituximab.

Abbreviations

ITP: Immune thrombocytopenia

CITP**: c**hronic immune thrombocytopenia

SCITP: severe chronic immune thrombocytopenia

HDD: high-dose dexamethasone

TR: total response

SR : sustained response

TPO-Ras: thrombopoietin receptor agonists

CR: complete response

R: response

BW: body weight

Background

Immune thrombocytopenia (ITP) is the most common bleeding disorder in childhood, characterized by autoantibody-mediated destruction of platelets. Skin and mucosal bleeding are the main clinical manifestations associated with ITP. In some patients, severe bleeding can occur, which in some cases can even lead to death. The first-line treatments for ITP include intravenous immunoglobulin (IVIG) and corticosteroids. Although these treatments have shown to be effective in most patients, approx. 20% of children with ITP do not respond well to therapy. In addition, some of those patients may develop spontaneous remission and, eventually, chronic immune thrombocytopenia (CITP).

Rituximab, thrombopoietin receptor agonists (TPO-Ras), and splenectomy have been approved as second-line therapy for ITP in children. According to recently published international authoritative guidelines (ASH [1] and ICR[2]), TPO-Ras should be the first selection, followed by rituximab. Splenectomy is rarely considered bearing in mind its invasiveness and association with some side effects. High-dose dexamethasone (HDD) has been recommended by 2019 ICR [2] as the first choice for persistent and chronic childhood ITP with severe bleeding. In China, eltrombopag has been commonly applied in the treatment of children with SCITP. It can be applied orally, for a longer time, without causing remission. Yet, this drug is expensive. Thus, the combination with immunosuppressants has become an important strategy for treating children with SCITP [3].

We have recently explored different treatment protocols for SCITP children and found that HDD has an effective rate of 45% (platelet count after treatment (30-100) $\times 10^9$/L and at least two times higher than the basal platelet count); bleeding symptoms improved in about 80% cases [4]. Moreover, we further examined low-dose rituximab treatment in those who did not respond well to HDD, and we found a drug response rate of 44% [5]. We recently examined eltrombopag for children with SCITP previously treated with corticosteroids, high-dose immunoglobulin, or rituximab treatment. The results showed 75% (15/20 cases) of response, 35% of complete response (platelet count is $\geq 100\times10^9$/L without bleeding), and 70% SR rate [6]. Based on international recommendations and our experience, we consequently designed the second-line escalating treatment strategy using HDD, low-dose rituximab to eltrombopag for children with SCITP. In this paper, we collected and analyzed the data from this treatment.

Materials and Methods

This study was a single-center, retrospective cohort study. The data of children SCITP who received escalating treatment strategy in the National Center for Children's Health of China were collected between June 2017 and August 2019. Informed consent was obtained from children or

their guardians. This retrospective chart review protocol was approved by the Beijing Children's Hospital. This study was registered on chictr.org.cn (ChiCTR-1900022419).

Inclusion/ Exclusion criteria

Inclusion criteria were the following: (1) age 1-14-year-old with SCITP (diagnosis was made following the diagnostic criteria of ICR in 2019 [2]); (2) first-line treatment was ineffective; (3) > 12 months duration of ITP with platelet count<30×10^9/L and frequent bleeding or parents/children in urgent need of treatment; (4) follow-up >12months in our clinic.

Exclusion criteria were: life-threatening bleeding at the beginning of this study, not being able to adhere to sequencing escalating treatment strategy, and those followed up for <12months.

Definition and Effectiveness assessment [1, 2]

Definition

Chronic immune thrombocytopenia (CITP) was defined as the duration of ITP > 12 months. Severe ITP was defined as platelet count <30×10^9/L with bleeding symptoms requiring treatment or new bleeding symptoms that require drugs that increase platelets. Severe chronic ITP (SCITP) was defined as CITP with severe ITP.

Bleeding classification

According to the 2019 ICR Expert Consensus[2], the bleeding scale for pediatric patients was updated with ITP: Grade 1 (minor): few petechiae (≤100 total) and/or ≤5 small bruises (diameter ≤3cm), no mucosal bleeding; Grade 2(Mild): a small amount of bleeding, more ecchymosis (total>100) and/or>5 large ecchymosis (diameter>3cm), no mucosal bleeding; Grade 3 (moderate): moderate bleeding, overt mucosal bleeding, troublesome lifestyle; Grade 4 (severe): severe bleeding, mucosal bleeding leading to decrease in hemoglobin 2 g/dL or suspected internal hemorrhage, belongs to the exclusion criteria.

Efficacy assessment

According to the efficacy judgment of ASH [1] in 2019, (1) Complete response (CR) was defined as the platelet count of ≥100×10^9/L without bleeding; (2) Response (R): the number of platelet count after treatment of (30-100) × 10^9/L and at least 2 times higher than the basal platelet count without bleeding; (3) no response (NR): the platelet count < 30×10^9/L or lower than the lowest platelet count 2 times, or with related clinical bleeding; (4) Total response: CR+R; (5) Remission: the platelet count at 12 months is > 100×10^9/L (regardless of treatment or not); (6) Sustained response (SR): platelet count ≥30×10^9/L, at least twice the baseline count at 6 months; (7) Relapse: ①

Relapse after remission: the platelet count decreased to < 100×10^9/L again in those who were at remission after 12 months of treatment; ② Relapse after SR: those who were assessed as SR after 12 months of treatment (up to 6 months after reaching >30×10^9/L), the platelet drops again and is less than 30×10^9/L. Total relapse: ①+②.

Escalating treatment strategy

Escalating treatment strategy was divided into 3 steps:

Step I: HDD (dexamethasone 0.6mg./kg/d, maximum dose 40mg/day, intravenously or orally), was used for 4 consecutive days, one course lasted 28 days for a total of 6 courses. If no response was observed after 2-4 courses, Step II was initiated. If R was reached, 6 courses were completed.

Step II: low-dose rituximab (body weight (BW)<30kg, 100mg; BW>30kg, 200mg, once a week, 4 times). If no response was observed during the 6th to the 12th week, Step III was started. If CR and R were reached, six courses of HDD were completed.

Step III: initiate eltrombopag at 50 mg once daily for the patients aged 6-17 years, and more than 27kg BW, 1.5 mg/kg once daily for aged 1-5 years (or <27kg) initially [6]. Platelet counts were assessed weekly for 2 weeks, and then every month after that. We allowed dose adjustments based on platelet response of at least doubling of the baseline count and absence of bleeding up to a maximum dosage of 75 mg per day. When the platelet count was <50×10^9/L for at least 2 weeks, the daily dose increased to 12.5 mg for children 1-5 years, while for children aged 6-17years old, a dose was increased by 25 mg. At platelet counts exceeding 150×10^9/L, the dose was reduced. When platelet counts were ≥200~400×10^9/L, patients taking 25 mg once daily decreased the dose to 12.5 mg once daily and 25 mg for the larger doses. We waited for two weeks to assess the effects of this and any subsequent dose adjustments. In patients who achieved platelet counts above 400×10^9/L, treatment was temporarily suspended, and blood counts were closely monitored. Once the platelet count was below 150×10^9/L, eltrombopag was reinitiated at a lower dose. Clinical hematology and liver regularly tests were monitored throughout therapy; the eltrombopag dosage regimen was modified based on platelet counts. All patients were informed about the potential adverse events. Appropriate administration of the drug and possible interaction with certain foods were explained.[6]

During the treatment, if an acute bleeding episode occurred and/or the platelet count was <10×10^9/L, 400-500 mg/kg of IVIG could be given temporarily.

Study method

Before starting treatment, data on gender, age, course of the disease, platelet count, bleeding score, and previous treatment were collected.

Observation indications and assessment points during the treatment were: Remission rate and SR rate of each step; Total response rate at different times: 12^{th}, $24^{th,}$ and 36^{th} month, and the relapse rate.

Statistical analysis

All patients were followed up until August 01, 2020. All statistical analyses were performed with the SPSS (version 19) software. Quantitative data with normal distribution were expressed as mean±standard deviation and were compared by the t-test. Those with skewed distribution were described as median (upper and lower quartiles) and compared by the Wilcoxon rank-sum test. Two-tailed $p<0.05$ was considered statistically significant.

Results

Baseline information

A total of 40 children with baseline data were included in the retrospective study; 10 children were excluded because they could not adhere to the treatment protocol. Finally, 30 cases were enrolled for analysis, 18 males and 12 females. The median age was 8.83 (1.42-13.9) years, and the ITP duration time was 20.5 (12-96) months. The median platelet count was 15 (3-30)$\times 10^9$/L; the bleeding rate was 6.7% (2/30) grade 1, 53.3% (16/30) grade 2, and 40% (12/30) grade 3（Table 1）. Previous treatments include 100% first-line treatment IVIG and once 40% (12/30) with short-term or irregular rituximab or domestic recombinant human TPO.

Distribution of escalating treatment strategy

The median follow-up time for children in this study was 14 (12-37) months. At the analysis point, the distribution (the remission rate) in Step I, II, and III was: 30.0% in 9/30 cases (33.3%, 3/9 cases), 13.3% in 4/30 cases (50%, 2/4 cases), and 56.7% in 17/30 cases (29.4%, 5/17 cases), respectively; 70% (21/30 cases) had at least one and 56.7% (17/30 cases) two escalated treatments (**Figure 1**).

Efficacy

Remission and response rate

The remission rate was 36.7% (11/30 cases): 27.3% (3/11 cases) in step I, 27.3% (3/11 cases) in step II, 45.4% (5 /11 cases) in step III. Moreover, remission distribution was 33.3% (3/9) for Step I: 50% (2/4) for Step II and 29.4% (5/17) for Step III. The SR rate was 68.2% (15/22 cases, the SR distribution was 46.7% (7/15 cases) in step I, 13.3% (2/15 cases) in step II, 40% (6 /15 cases) in step III.

The TR and remission rates at 12th were 80% (24/30 cases) and 36.7% (11/30 cases), 7 cases beyond 24th month observation point, the TR and remission rates were 57.1% (4/7 cases) and 28.6% (2/7 cases). Only 2 cases beyond 36th month observation point, the TR and remission rates were 50% (1/2 cases) and 50% (1/2 cases)(**Figure 2**).

The effective of TRAs

In the eltrombopag (step III) group, 29.4% (5/17) were in remission, 47.5% (8/17) maintained platelet count > 50×10^9/L with 37.5% (3/8) dose tapering, and 25% (2/8) were successfully discontinued from medication.

Relapse

Among 11 cases who reached remission, the relapse rate was 45.5% (5/11) with 2 cases (100%, 2/2) from Step II and 3 cases (50%, 3/6) from Step III; the median relapse time was 5 (1-12) months after reaching remission.

Among 15 cases who reached SR in 12months, the relapse rate was 20% (3/15) with one case (50% , 1/2) from Step II and 2 cases (33.3%,2/6) from Step III with 18 (17-24) months.

The total relapse rate was 26.7%(8/30) , three cases(75%, 3/4)from Step II , all of they were males and 5 cases (41.7% , 5/12) from Step III, none in Step I.

Discussion

Our study showed that this second-line escalating strategy might be effective in treating children with SCITP (effective rate with 36.7% remission and 68.2% SR rate). Previous studies [5, 7-9] have shown that low-dose rituximab may be beneficial for patients with CITP. Moreover, Ahmad *et al* [7] reported that a combination of HDD, rituximab, and CSA treatment for patients with CITP , the SR rate was 75%, and the treatment-free survival at 12 and 24 months was 93.3% and 80%, respectively. Similar results were reported by Choi *et al* [8], who found that 60% (12/20) of patients were in remission for more than 7 months without the need for any additional treatment. By contrast, Oved *et al* [9] reported SR in 30% of children with persistent or CITP treated with rituximab combined with three dexamethasone courses; SR was maintained for at least 60 months. Another study [10] investigated 37 refractory ITP patients, among 10 patients treated with immunosuppressive drugs plus TPO-Ras, seven (50% CR, 20% R) achieved continued treatment response, and only 1 (7.1%) had a CR. The above data suggest that the combination treatment is effective for patients with C/RITP. Moreover, SCITP treatment should include TPO-Ras, which can stimulate platelet production in combination with the immunosuppressant.[11]

In our study, 30% of the children could benefit from HDD and remain stable during follow-up without experiencing relapse. Thomas *et al* [12] reported that 78% of patients with CITP achieved remission within 3 days after HDD therapy, while long-term remission was found in less than half of cases. Nugent *et al* [13] reported that the remission rate in 18 CITP children treated with HDD after one year was 44%. Furthermore, Youssef *et al* [14] found that HDD is an emergency treatment for uncontrolled bleeding in chronic ITP children. In their study, approx. 80% of bleeding symptoms were controlled by HDD. Consistently, our data shows that HDD can be effective for SCITP treatment, and some patients can stabilize from HDD and do not require further second-line treatment (as rituximab and TPO-Ras) to avoid overtreatment.

In our study, 47.5% of patients treated with HDD, rituximab and eltrombopag (step III), had sustained response with platelet $\geq 50\times10^9$/L; dose tapering was observed in 37.5% cases, and 25% were successfully discontinued from medication. Our data showed a higher response rate in those treated with immunosuppressants combined with TPO-RA. Grainger *et al* [15] found a sustained platelet response in 40% of patients with CITP treated with eltrombopag. Similar data were reported by Cheng *et al* [6]. Bussel and colleagues [16] treated 45 CITP patients with eltrombopag; 62% of cases had a platelet count of at least 50×10^9/L without salvage. After the application of TPO-Ras for CITP [17], overall pooled effect analysis of the five RCTs results favored TPO-Ras over placebo (RR=4.31; 95%CI[2.45–7.58];P<0.00001). Gómez-Almaguer *et al* [18] assessed the safety and efficacy of the combination of eltrombopag, low-dose rituximab, and dexamethasone in 13 newly diagnosed ITP patients. The ORR was 100%, with a 92% CR rate and a relapse-free survival rate of almost 80% at 12 months. To sum up, a higher response rate was achieved with immunosuppressant treatment combined with TPO-RA.

Rituximab has been associated with a high relapse rate in children with ITP. Previously, Kousaku *et al* [19] reported on a long-term effect of rituximab in 22 pediatric ITP patients. CR was achieved in 41% of patients within 2 months, while 72.7% (8/11) relapsed during 2-26 months after initial treatment. In a multicenter, randomized trial [20] the relapse rate was 50% in a rituximab group. Another Dutch trial [21] compared three rituximab dosing schemes in 156 patients with relapsed or refractory ITP; the response rates were similar within the three arms (63%, 59%, and 61%, respectively), with a relapse-free survival of 72% at 1 year and 58% at 2 years. Petel *et al* [22] examined the long-term effect in 66 children and found that 58% had a continuous response for at least 1 year, among whom only 15.8% relapsed after 1 year. Moreover, Matsubara and his team [19] found 72.7% of patients relapsed 2–26 months after initial rituximab treatment from refractory ITP children. The 5-year relapse-free rate was 14 % (3/22, 95 % confidence interval: 0–27 %) with a median follow-up period of 6.4 years. Our results revealed a total relapse rate of 26.7%, higher relapsed rate in Step II(all of they were males). Similar to the research by Oved et al[9], they administered rituximab and dexamethasone to children with persistent CITP and found that 66.6% of male patients relapsed within 3 years. Maybe female patients respond longer to

rituximab. The relapse rate in Step III was lower than the rate in Step II, while no relapse was observed in Step I (HDD). The data showed that although rituximab is an effective second-line treatment drug, its curative effect is limited and tends to relapse when the drug effect disappears, thus highlighting the need for salvage treatment. TPO-Ras drugs can effectively increase the curative effect and reduce relapse. Eltrombopag may be effective for patients' who do not respond well to HDD and rituximab treatment, reflecting the value and significance of combined therapy.

This study has a few limitations. This is a retrospective cohort study. Also, children follow-up for less than 1 year were excluded from the study. The sample size was small, and the observation time was not long enough.

There are also some unresolved problems in the present study: 1) at present, HDD is widely recommended first-line treatment (reference); it remains unclear whether HDD could reduce the evolution of SCITP; 2) with the high relapse rate, what is the significance of rituximab using? When should it be used? Should TPO-Ras combined with rituximab be used in advance to achieve better efficacy? All these questions need to be further explored.

In conclusion, this second-line escalating strategy for children SCITP has an effective improving rate with 36.7% remission and 68.2% sustained response rate; 30% of patients could benefit and obtain stable response after HDD treatment. However, low-dose rituximab has been associated with a high relapse rate, patients who failure to HDD combining low-dose rituximab would be benifit with eltrombopag.

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