DOI: 10.24287/1726-1708-2020-19-3-26-30

Received 07.04.2020
Accepted 27.07.2020

Treatment lines of childhood chronic ITP: A retrospective single-center analysis

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Immune thrombocytopenia (ITP) is the most common cause of thrombocytopenia in children. Approximately 20–25% of children develop a chronic course of the disease. Many treatment options are available, including chronic use of first-line therapies, e.g., corticosteroids, intravenous immunoglobulin or anti-Rh-D, and second-line therapies, including dexamethasone, high-dose methylprednisolone, intensive immunosuppressants, rituximab, thrombopoietin receptor agonists (TPO-RAs), splenectomy, and many others; however, none of these treatments have been determined to be the best. In this study, we retrospectively reviewed the course, response to different treatment lines and outcome of children with chronic ITP over a period of ten years to compare the efficacy of different treatment options, aiming to determine a scale of priority for selecting the most cost-effective treatment. A retrospective study was conducted and included children diagnosed with chronic ITP from January 2008 until December 2018 who were followed at the Pediatric Hematology Unit of Mansoura University Children Hospital, Mansoura, Egypt. The study proposal was approved on February 14, 2017 (approval No 17.02.59) by the Institutional Review Board (IRB) of the Faculty of Medicine, Mansoura University, Egypt. All research steps were conducted according to the Declaration of Helsinki. The diagnosis of chronic ITP was based upon the persistence of thrombocytopenia lasting for more than 1 year with or without therapy. Bone marrow aspiration was performed for all patients to confirm the diagnosis of chronic ITP and exclude other causes of thrombocytopenia. Data relevant to chronic ITP patients diagnosed from 2008 to 2018 were retrieved from the Electronic Data System of Hospital Management of Mansoura University Children Hospital, including age, sex, diagnosis date, duration of chronicity, treatment given during the chronic phase and response. Treatment regimen was immune modulatory therapies (high-dose dexamethasone, IV rituximab or low-dose dexamethasone + azathioprine), thrombopoietin receptor agonists (TPO-RAs) (eltrombopag or romiplostim). Out of 405 newly diagnosed ITP patients in a period of 10 years in our center, 103 progressed to chronic disease, of whom 29 were lost to follow-up, while 74 patients were followed at the hematology outpatient clinic and enrolled in the current study (32 males and 42 females, median age – 10 years, median initial platelet count – 16 × 10^9/l). Approximately one-third of patients (25~33.8%) were managed conservatively; of them, 19 patients achieved sustained remission, and 6 patients needed another treatment line. Forty-six (62%) patients received immunomodulatory therapies. Twenty-eight patients (37.8%) were treated with TPO-RAs. No differences were observed between the 3 types of immunomodulatory therapies regarding relapse-free survival and duration of remission (*p* value: 0.7). Additionally, no differences were noted according to relapse-free survival among those treated with eltrombopag and romiplostim (*p* value: 0.7). The number of male children who had a sustained response was significantly higher than that of female children among patients receiving immunomodulatory therapies (71.4% vs 28.6%, respectively) (*p* value 0.01). There were significantly more patients on TPO-RA with a sustained response than patients on immune modulators, and consequently, the number of patients who relapsed on immunomodulators was higher than that of those on TPO-RA (67.9% vs 30.4% compared to 69.9% vs 32.1%, *p* value 0.01). Many of our patients who received immunomodulators and failed to achieve or lost a response before 2015 were switched to TPO-RAs with comparable efficacy apart from sustainability, which was in favor of the latter. Additionally, among the types of immunomodulators, rituximab did not show superior efficacy compared to other types, with lower costs for the latter, leading to the abandonment of its use, particularly in limited resource countries such as ours.

Key words: *immune thrombocytopenia, immunomodulators, thrombopoietin receptor agonists, sustained response, complete response, partial response*

Yasser A., et al. Pediatric Hematology/Oncology and Immunopathology. 2020; 19 (3): 26–30.
DOI: 10.24287/1726-1708-2020-19-3-26-30

Immune thrombocytopenia (ITP) is the most common cause of thrombocytopenia in children [1]. Although the disease is self-limited in most children, with a resolution rate of 80% of patients within 6–12 months from diagnosis, approximately 20–25% of children develop a chronic course of the disease [2]. The goal of treatment for chronic ITP is to provide a safe platelet count that prevents major bleeding, rather than achieving a normal platelet count [3]. Many treatment options are available, including chronic use of first-line therapies, e. g., corticosteroids, intravenous immunoglobulin or anti-Rh-D, and second-line thera-

pies, including dexamethasone, high-dose methylprednisolone, intensive immunosuppressants, rituximab, thrombopoietin receptor agonists (TPO-RAs), splenectomy, and many others [4]; however, none of these treatments have been determined to be the best [5]. In this study, we retrospectively reviewed the course, response to different treatment lines and outcome of children with chronic ITP over a period of ten years to compare the efficacy of different treatment options, aiming to determine a scale of priority for selecting the most cost-effective treatment.

MATERIALS AND METHODS

A retrospective study was conducted and included children diagnosed with chronic ITP from January 2008 until December 2018 who were followed at the Pediatric Hematology Unit of Mansoura University Children Hospital, Mansoura, Egypt. The study proposal was approved on February 14, 2017 (approval No 17.02.59) by the Institutional Review Board (IRB) of the Faculty of Medicine, Mansoura University, Egypt. All research steps were conducted according to the Declaration of Helsinki. The diagnosis of chronic ITP was based upon the persistence of thrombocytopenia lasting for more than 1 year with or without therapy [6]. Bone marrow aspiration was performed for all patients to confirm the diagnosis of chronic ITP and exclude other causes of thrombocytopenia. Data relevant to chronic ITP patients diagnosed from 2008 to 2018 were retrieved from the Electronic Data System of Hospital Management of Mansoura University Children Hospital, including age, sex, diagnosis date, duration of chronicity, treatment given during the chronic phase and response.

Classification of management lines during the chronic phase:

- Conservative: No pharmaceutical treatment was needed.
- Second-line therapy:

– Immune modulatory therapies: high-dose dexamethasone, IV rituximab or low-dose dexamethasone (1 mg/day) + azathioprine.

– Thrombopoietin receptor agonists (TPO-RAs): eltrombopag or romiplostim

Definitions of treatment response:

Complete response (CR): A platelet count > 100 × 10^9/L, measured on two occasions seven days apart and the absence of bleeding [7].

Partial response (PR): A platelet count > 30 × 10^9/L or more than a two-fold increase in platelet count from baseline, measured on two occasions, seven days apart and the absence of bleeding [7].

No response (NR): A platelet count < 30 × 10^9/L, a less than 2-fold increase in platelet count from baseline or the presence of bleeding. Platelet count must be measured on two occasions more than a day a part [7].

Loss of response (LR): A platelet count < 30 × 10^9/L, a less than 2-fold increase in platelet count from baseline or the presence of bleeding after achieving an initial complete/partial response. Platelet count must be measured on two occasions more than a day a part [7].

Sustained response: A sustained response was considered when the patient attained CR or PR until the end of the study.

RESULTS

Out of 405 newly diagnosed ITP patients, 103 progressed to chronic disease, of whom 29 were lost to follow-up, while 74 patients were followed at the hematology outpatient clinic and enrolled in the current study. Clinicolaboratory features of the studied group are shown in *table 1*.

Figure 1 demonstrates the lines of treatment given for the studied patients during the chronic phase.

Table 1
Clinicolaboratory features of the studied patients

Features	Studied group (*n* = 74)
Age in years: Median (Min–Max)	10 (2.5–18)
Sex, *n* (%): Male Female	 32 (43.2) 42 (56.8)
Age of initial presentation (years): Median (Min–Max)	6 (0.5–14.5)
Duration of disease (years): Median (Min-Max)	3 (1–10)
Initial platelet count (× 10^9/L): Median (Min–Max)	16 (0–76.0)
Need for rescue therapy*, *n* (%)	49 (66.2)

*Note. * – means treatment given to control breakthrough bleeding episodes during the chronic phase.*

Approximately one-third of patients (25~33.8%) were managed conservatively; of them, 19 patients achieved sustained remission, and 6 patients needed another treatment line. Forty-six (62%) patients received immunomodulatory therapies (rituximab, high-dose dexamethasone and azathioprine + low-dose dexamethasone). Twenty-eight patients (37.8%) were treated with TPO-RAs.

No differences were observed between the 3 types of immunomodulatory therapies regarding relapse-free survival and duration of remission (*p* value: 0.7) (*figure 2*). Additionally, no differences were noted according to relapse-free survival among those treated with eltrombopag and romiplostim (*p* value: 0.7) (*figure 3*).

In *table 2*, the number of male children who had a sustained response was significantly higher than that of female children among patients receiving immunomodulatory therapies (71.4% vs 28.6%, respectively) (*p* value: 0.01). There were significantly more patients

Figure 1
Scheme for treatment lines used for chronic ITP patients

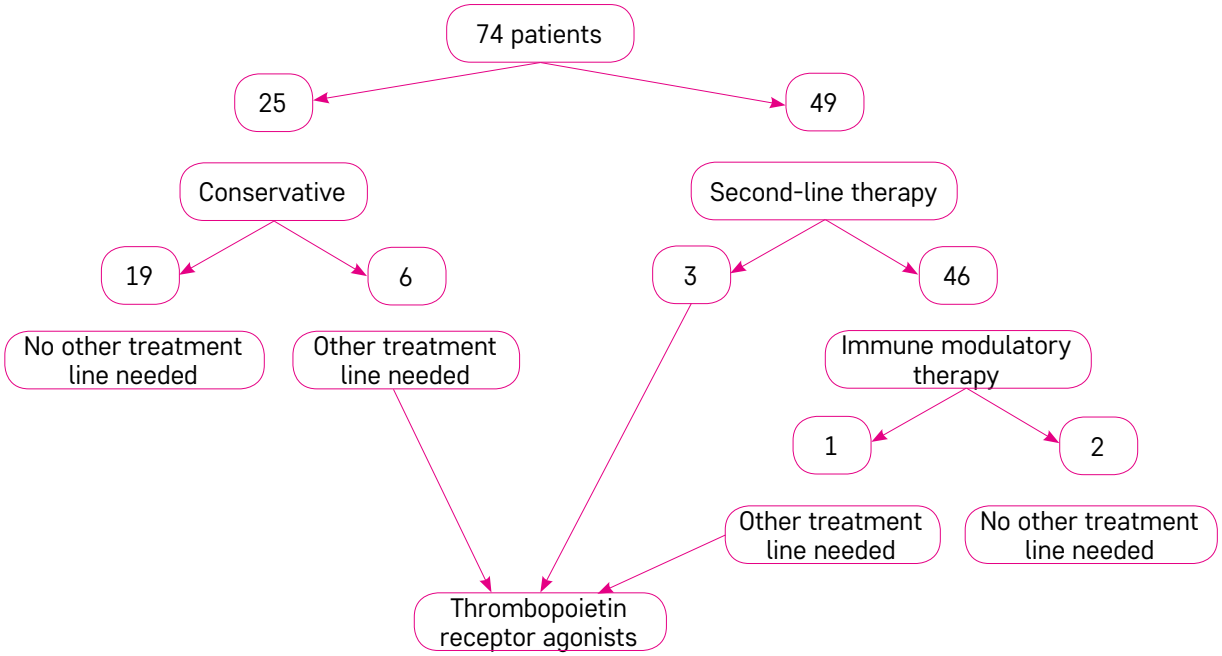


Figure 2
Kaplan–Meier analysis of relapse-free survival for different immunomodulatory therapies. There was no significant difference between them (*p* value: 0.7); the proportion of relapsed patients treated with azathioprine + low-dose dexamethasone at 9 months was 10%, while 30% of patients treated with rituximab relapsed within 8 months. Additionally, 16% of patients treated with high-dose dexamethasone relapsed within 36 months

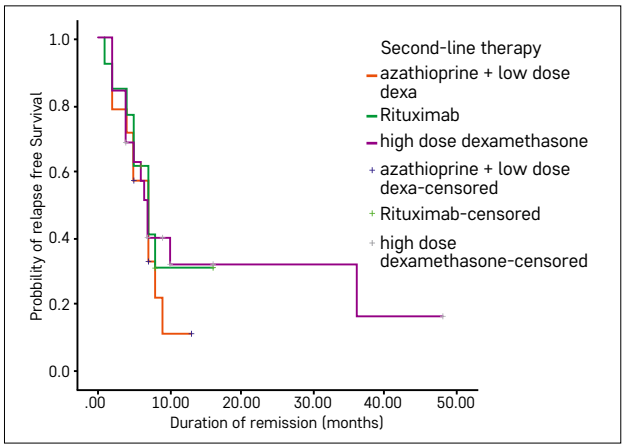
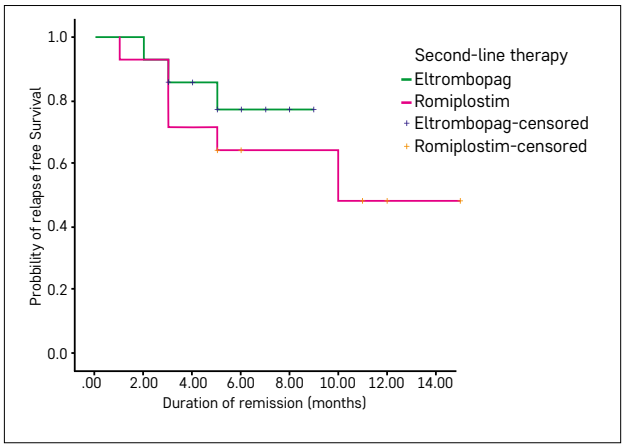


Figure 3
Kaplan–Meier analysis of relapse-free survival of thrombopoietin receptor agonists. There was no statistically significant difference between the two groups (*p* value: 0.7); 53% of patients treated with eltrombopag relapsed within 10 months, while 71% of patients treated with romiplostim relapsed within 2 months



on TPO-RA with a sustained response than patients on immune modulators, and consequently, the number of patients who relapsed on immunomodulators was higher than that of those on TPO-RA (67.9% vs 30.4% compared to 69.9% vs 32.1%, *p* value: 0.01) (*table 3*).

DISCUSSION

ITP is a common autoimmune disorder known to have a benign course in many children [8], yet 5–10% of chronic cases lead to serious bleeding, and the treatment of these patients remains a real challenge [9]. Since there is no consensus on the management of chronic ITP in children, the treatment depends largely on clinical expertise and observations [10].

In the present study, we analyzed the response to different treatment lines given for chronic ITP patients in our institute over the last 10 years by conducting a retrospective cohort study. There were more females than males (56.8%). This is similar to previous studies showing female predominance in chronic ITP patients, supporting the idea that female sex is a risk factor for chronicity [11–13]. The median age at initial presentation was 6 years, which emphasized what Güngör et al. [14] found: the main age of presentation for childhood ITP ranged from 2 to 10 years.

Table 2
Patients' clinical characteristics in relation to their response to immunomodulatory therapy

Clinical features	Sustained response	Lost response	*p* value
Age in years: Mean (SD)	10.3 (3.8)	10.4 (4.1)	0.7
Age of disease onset: Median (Min–Max)	8.5 (0.5–12.5)	6 (0.5–14.5)	0.8
Sex, *n* (%): Male Female	10 (71.4) 4 (28.6)	10 (31.3) 22 (68.8)	0.01
Disease duration: Median (Min–Max)	2 (1.5–9.5)	3 (1.5–10)	0.3

Table 3
Comparison between immune modulators and thrombopoietin receptor agonists according to patients' response

Treatment Response	Immune modulators *n* = 46	Thrombopoietin Receptor Agonists *n* = 28	*p* value
Complete response, *n* (%)	9 (19.6)	13 (46.4)	0.09
Response, *n* (%)	24 (52.2)	10 (35.7)	0.9
No response, *n* (%)	13 (28.3)	5 (17.9)	1
Sustained response, *n* (%)	14 (30.4)	19 (67.9)	0.01
Loss of response, *n* (%)	32 (69.6)	9 (32.1)	
Remission duration, months Median (Min–Max)	6.2 (1–48)	6 (1–15)	0.7

Approximately one-third of patients (33.8%) were managed conservatively, and a large portion of these children achieved remission. This supports the idea that children will likely recover within an additional 1–2 years [15]. Furthermore, these results are consistent with the current guidelines suggesting that observation is a safe alternative for children who do not experience serious bleeding and limits the indication for the use of platelet-enhancing therapies [16].

No difference in response to immunomodulatory therapies was noted. Although many researchers have studied the effect of combined rituximab and high-dose dexamethasone in the treatment of chronic ITP with satisfactory results [17, 18], to the best of our knowledge, we did not find previous studies comparing the efficacy of different immune modulatory therapies.

The initial response rate to rituximab was approximately 54%; however, only 15% of patients maintained remission. Although the response to rituximab was encouraging for many patients, the sustainability of remission is difficult. Patel et al. [19] reported an initial 57% response rate to rituximab, but the sustained response was only 26%. It was thought that relapse is secondary to the return of B cells to higher levels than those in individuals who never relapsed [20]. In this study, the male response to immunomodulatory therapy was greater than that of females. Similarly, Chapin et al. [18] found a better male initial response to combined rituximab and high-dose dexamethasone in adults with ITP; nevertheless, this was not observed in children. This was not agreed upon by Jayabose et al. [21], who did not find prognostic significance for sex in relation to response to treatment with WinRho, IVIG or steroids in children with chronic ITP.

No differences were reported in response or sustainability of response between both types of TPO-RAs (eltrombopag and romiplostim). Our results are consistent with those of a systemic review analyzing five randomized controlled trials studying the efficacy and safety of eltrombopag and romiplostim in children with persistent and chronic ITP, and no difference was noted between the two types [22]. Although both TPO-RAs showed good initial response, approximately one-third of our children lost their response to each type of TPO-RA. The sustainability of remission with the use of TPO-RAs is not as high as the short-term response. This is in agreement with previous studies reporting that the long-term response was much lower than the short-term response, reaching 30% compared to 90% for the initial response [23–25].

Our study reflects the variability in treatment options for chronic ITP. Additionally, the priority of selecting second-line therapy in the era of TPO-RAs and approval of eltrombopag for children in 2015 as well as the approval of off-label use of romiplostim were changed [26, 27]. Many of our patients who received immunomodulators and failed to achieve or lost a response before 2015 were switched to TPO-RAs with comparable efficacy apart from sustainability, which was in favor of the latter. Additionally, among the types of immunomodulators, rituximab did not show superior efficacy compared to other types, with lower costs for the latter, leading to the abandonment of its use, particularly in limited resource countries such as ours.

Although many treatment options are available for chronic ITP, to date, no single therapy can suit all patients. Further studies are ongoing to identify new medications for difficult unresponsive cases.

FUNDING
Not specified.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

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