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Chronic immune thrombocytopenic purpura in children overview of 60 patients

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ABSTRACT

Background: A small percentage of children with Immune thrombocytopenic purpura (ITP) suffer from a clinically significant disease with severe thrombocytopenia that requires intervention. Treatment for these children presents a challenge as there are few known therapies that offer long-term remission, and all that are known have significant side effects and toxicities.
Aim of the study: To evaluate the effects of a variety of treatment modalities on the clinical course, and long treatment outcomes in children with chronic ITP.
Patients & methods: A study involved 60 children with chronic ITP who were referred to Hemato-Oncology unit/Children's Welfare Teaching Hospital/Medical City/Baghdad. Treatment of patients included steroid, Intravenous Immunoglobulins, Anti D immunoglobulin, 6-Mercaptopurine, Rituximab and splenectomy. The Period of data collection and analysis was from May 2009 to May 2011.
Results: The most common presenting symptom was skin bleeding, seen in 42 (70%) patients. Thirty-four patients received one or more courses of steroids. Complete response was achieved in 7 (20.5%) patients while there was no response in 12 (35.2%) patients, Intravenous immunoglobulin was used for 5 patients, only one (16%) exhibited a good response. Anti D Immunoglobulin was used in six patients; only one (8.3%) patient got good response. Twelve patients received 6-mercaptopurine, only one (8.3%) patient had a partial response. Six patients received Rituximab; three (50%) had a partial response. Six patients underwent splenectomy; response was noted in 5/6 (83.3%) patients. At the end of the study; complete response was seen in 13 (22.4%) patients, partial in 19 (31.6%), no response in 28 (46.7%) patients.
Conclusions: Splenectomy is the most effective treatment modality when treating children with chronic ITP whose symptoms are severe.

1. Introduction

Immune thrombocytopenic purpura (ITP), is an acquired autoimmune disorder defined by isolated thrombocytopenia and the exclusion of other causes of thrombocytopenia [1]. Acute ITP is the most common cause of thrombocytopenia in children. Peak occurrence is between 2 and 5 years of age. In most children with acute ITP the disease is self-limited, with resolution in 80% of patients within 6–12 months from diagnosis [2]. Only a small subset of children with ITP have a clinically significant disease with severe thrombocytopenia and/or bleeding that requires intervention [3].

Persistent thrombocytopenia, will continue in 20–30% of children with acute ITP but nearly 25% of children with ITP will recover within 12 months from the date of diagnosis [4]. Patients with chronic refractory ITP are clinically heterogeneous. Some have recurrent, severe bleeding, but most have intermittent, mild bleeding. Some patients will have spontaneous, permanent

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remissions at some time during the course of the disease, never the less, most patients, will continue to have thrombocytopenia [5].

2. Aim of the study

To evaluate the effects of various treatment modalities on the clinical course, and long term outcome in children with chronic ITP.

3. Materials and methods

The study was involved 60 patients referred to the Hemato-Oncology unit/Children's Welfare Teaching Hospital (CWTH)/ Medical City/Baghdad with chronic ITP, defined as having platelets count of $<100 \times 10^9$/L for more than 6 months without identifiable cause [6]. Data was collected from 1st of May 2009 until mid-May 2011. In addition to a detailed history and physical examination, the diagnostic studies at CWTH included a full blood count, evaluation of the stained peripheral blood smear, bone marrow aspiration, biochemical profile, routine tests of hemostasis, and antinuclear antibody for collagen vascular diseases. Up until 2009 at CWTH; steroid was the main– if not the only– option for treatment of ITP. After that treatment, including other agents, was individualized according to availability, the status of the disease and family consent.

3.1. Treatment options given to children with chronic ITP during the study period include:

First line Treatment [6]:

1 Steroids
   a. Prednisolone 1–2 mg/kg/day for 2–4 weeks
   b. Methylprednisolone 500 mg/m^2/day for 3days
   c. Dexamethasone 4 mg/kg/day or 40mg/m^2/day (maximum 40 mg) IV infusion for 3 days
   d. Prednisolone 4 mg/kg/day for 4 days
   e. Prednisolone 0.5 mg/kg every other day for several weeks up to 6–12 months
2. Intravenous Immuno-Globulin (IVIG); 1–2 g/kg Intravenous infusion over 4 h
3. Anti-D Immunoglobulin 50 μg/kg single dose IV infusion over 1 h or Intramuscular in the lateral aspect of the thighs.

Second line Treatment [6].

4. Mercaptopurine (6 MP); 50 mg/m^2/day single time orally for 4–12 months according to response.
5. Rituximab 375 mg/m^2/dose every week for 4 doses, If failed first line or second line treatment:

6 Splenectomy

The following measures were done before and after splenectomy:

1. Pneumococcal vaccine given at least 2 weeks before surgery
2. Dexamethasone 40mg/m^2/day Intravenously in two divided doses over 3 days before surgery
3. Infusion of single donor platelets unit in the early morning with checking of platelet's count 1 h after completing the infusion, with another two units prepared standby.
4. After splenectomy; the patients kept on Benzathin penicillin 1.2 mega unit Intramuscular every 4 weeks.

3.2. Response to therapy: Defined as follows:

I. A complete response (CR) was defined as return to normal platelet count (greater than 150×10^9/L) during or after therapy.
II. A partial remission (PR) was defined as an increase in the platelet count to greater than 50×10^9/L.
III. No response (NR) was defined as no response to therapy with continued platelet count below 50×10^9/L. [7].

4. Statistics

Calculations of means, medians and routine statistical measures were performed by the mathematical component of the Microsoft Excel spreadsheet program.

5. Results

Sixty patients were identified during the study period; they were referred either from other hospitals, or those who were already treated at CWTH. One patient was suffering from ITP since 1997 and the others were diagnosed after 2002. The median age at time of diagnosis was 5 years, mean age was 5.5 years (range 8 months–11.6 years). The peak age was 4 years. There were 25 (41.6%) boys and 35 (58.4) girls. The male-to-female ratio was 0.7:1. There was a wide range of variation in the duration of symptoms ranging from 1 day to 11 years. One patient was found to have low platelet count during preoperative investigation for cochlear implant due to congenital deafness.

5.1. Clinical presentations

The common presentation signs were skin bleeding alone in 41 (68.3%) patients followed by skin and mucous membrane in 17 patients (28.2%), one patient had hematoma after intramuscular injection of vaccine, and one patient had no bleeding or complaint. The median platelet count at initial presentation was 10×10^9/L, mean 16, 8×10^9/L (Range: zero to 69×10^9/L). Bone Marrow Aspirates at time of diagnosis was done in 49 (81.6%) patients before commencing steroids, the results were normal, 11 patients missed this evaluation for unknown reasons. At re-evaluation at CWTH; 35 patients underwent BMA as mandated by clinical assessment and only one patient did not do the BMA neither at diagnosis nor at presentation to CWTH.

Coombs and Anti-nuclear antibodies were negative in all patients at time of re-evaluation at CWTH.

5.2. Treatment of patients having chronic ITP

Oral steroids were generally the preferred/obligated agents in patients treated in the study period. In patients who were refractory to steroids, those who became steroid-dependent to stay in remission, and those who relapsed, other options were tried (Table 1).

Table 1
Response to different treatment modalities in chronic ITP.

Type of Drugs		No.	Response		
			Complete	Partial	None
1.	Steroids (one or more courses)	34	7 (20.6%)	15 (44.1%)	12 (35.3%)
2.	IVIG	5	1 (20%)	0	4 (80%)
3.	Anti D	6	1 (16.6%)	0	5 (83.3%)
4.	Rituximab	6	0	3 (50%)	3 (50%)
5.	6 MP	12	0	1 (8.3%)	11 (91.6%)
6.	Splenectomy	6	5 (83.3%)	0	1 (16.6%)

IVIG: Intravenous Immunoglobulin, 6 MP: 6 Mercaptopurine.

First line treatment:

I. **Steroids therapy:** Thirty-four patients received one or more than one course of steroid; complete response was achieved in 7 (20.5%) patients while no response in 12 (35.2%) patients, there was no response in 15 (44.1%) patients.
II. **IVIG**: Used for 5 patients, one (20%) patient showed complete response, and 4 (80%) didn't show any response.
III. **Anti D:** Used for 6 patients who were Rh+ve, the main indication was recurrent generalized ecchymosis and mucous membrane bleeding. Only one (16.6%) patient got complete response, while5 (83.3%) showed no response.

Second line treatment:

I. **Mercaptopurine (6MP)**: Used for 12 patients received 6 MP at CWTH for a median period of 4.5 months, range (1–11 months). Only one (8.3%) patient showed partial response, he didn't need any further treatment.
II. **Rituximab:** Used for 6 patients. Duration of assessment of response was 8–9 months after initial dose of rituximab, three (50%) patients got partial response and they were free of symptom at time of last evaluation.
III. **Splenectomy:** Six patients underwent splenectomy after failure of other modalities of treatment (first or second line treatment), the median age was 11.5 years (range 6.7–15.7years). Menorrhagia was the main indication for splenectomy in the females while epistaxis was the main one in males. The median duration of illness before doing splenectomy was 3 years (range 1.7–13.3 years). Immediate response was noted in 5/6 patients with increment of platelet's count to a median of 325×10^9/L (range $156–625 \times 10^9$/L) within two days from splenectomy with no surgical complication during or after splenectomy.

6. Overall outcome

The median duration of chronic illness in those patients was 21 months (range 2–164 months) at time of last evaluation. Follow up period: median 20.5 months, (range 1–164 months), 10 patients were lost to follow up in 2009 and 2010, while the rest continued follow up till the end of the study period. Final response: Complete response was seen in 13 (22.4%), partial in 19 (31.6%), no response in 28 (46.7%) (Table 2).

7. Discussion

Immune thrombocytopenic purpura is a common hemorrhagic disease in childhood, with a heterogenous presentation and response to therapy during childhood. It is likely that all pediatricians will encounter children with ITP at some time in their practice [7]. Patients with acute ITP are not usually followed by the pediatric hematologist at CWTH. The benign nature of the disease makes it difficult for families to accept the idea of admission to the oncology unit. It was not possible to know the exact number and thus the percentage of children with chronic ITP for the purpose of this study as some patients were referred to CWTH while in a chronic phase. While the number of children involved in this study is fairly small, it might nonetheless be helpful in highlighting some distinctive behaviors and management problems with this particular group of patients. The median age of patients at time of diagnosis was 5 years (mean 5.5 years), the peak age was 4 years. A large-scale study done in China by Zhao H. involving 472 consecutive Chinese children with chronic ITP (age 1–14 years) showed the same peak age of 4 years [8]. There are other studies of patients with chronic ITP that show a higher median age at time of diagnosis [7,9]. The difference in the median age might be attributed to wider age range in other studies. In the current study; there were 25 boys and 35 girls. The male-to-female ratio was 0.7:1. There is similar, slight female predominance reported in other studies [7,9–11]. There is an extreme variable in the duration of symptoms from the time of diagnosis of ITP in our study ranging from 1 day to 11 years. The study by Wong MS reported a similar range (0–520) weeks [9]. The symptoms might endure over long periods due to a delay in diagnosis. This could be attributed to the somewhat insignificant symptoms presenting in the patient and the fact that the family is unaware that the child is sick. There was an absence of intracranial bleeding in this study group. This might be explained by a bias in referral as most of patients came from other hospitals and were in relatively stable condition. Or it might be simply be a reflection of the benign course of the chronic ITP as reported in the study by Glanz J which showed cutaneous bleeding in 52/60 (88%) patients, mucosal in 9/60 (23%) patients and no patient got internal bleeding [10]. while Kühne T study showed more aggressive presentations in Asian and European groups of children [12].

7.1. Response during chronic phase

In the current study, the CR to steroids was 20.6% which is lower than reported in other studies [8,9], this might reflect a refractory behavior in our group. The response to single course of IVIG in our study was similar to the steroid response, Wong [9] shows a lower response of 14.3%. the number of patients in both studies is small for evaluation. Aronis [13] showed a better response 10/26 (38.5%) after variable courses of IVIG (range 3-7courses).

Our results with anti D were not satisfactory, other studies showed more optimistic responses [14] but they were using more than one course of anti-D. In our study; the response to 6 MP was not satisfactory after having a variable periods of treatment in response to side effects or when the family refused extended/continued us of the drug. There are few published studies on the use of 6 MP in children with much better results (80–85%) than ours [15,16]. In our study the best result was with splenectomy where the response rate was 83.3%. the numbers are small but significant in light of the many technical and logistical obstacles we faced. Other studies present similar results with a response rate of 66.7–100% [8,11,17–19]. Our study showed a partial response to rituximab in 50% patients, the rest were non responders. There are few studies published showing the effect of rituximab in children with chronic ITP; Bennett CM et al. [20] showed a response in 7/30 (23%) children with chronic ITP.

7.2. Overall outcome

There were 28 (46.7%) non-responder patients; six (10%) patients remained asymptomatic while 22 (80%) had variable bleeding. None of our patients had CNS bleeding or died from any cause in addition to bleeding during the period of follow.

Table 2
Overall outcomes.

Response	No.	%	Clinical status
CR	13	22.4	No bleeding
PR	19	31.6	Ecchymosis in 1, no bleeding in 16, unknown in 2
NR	28	46.7	No bleeding in 6, ecchymosis in 12, epistaxis in 4, menorrhagia in 1, unknown in 5

Similar results were reported in other studies which show 40–55% still having significant thrombocytopenia during the period of the study [7,19]. on the contrary some studies showed better responses (62.6%) with significant number of them underwent splenectomy [11].

8. Conclusions

1. In children with chronic ITP with severe symptoms and significant thrombocytopenia, splenectomy is the most effective treatment with minimal immediate complication; still late complications require a longer follow up period.
2. About half of children with chronic ITP in this study achieved remission.
3. Rituximab therapy is beneficial for some children with severe chronic ITP who are refractory to standard agents.

Conflict of interest

The authors declare no conflict of interest.

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