CLINICAL STUDY

Immune thrombocytopenic purpura in children

Hostynova E, Cap J, Lukac J, Raskova J, Kadrliakova A, Zednickova N, Bodova I

Department of Haematology and Transfusiology of Children's University Hospital, Comenius University, Bratislava, Slovakia. **hostynova@dfnsp.sk**

Abstract

Immune thrombocytopenic purpura (ITP) is the most commonly acquired bleeding illness in children. 70—80 % of children resolve from acute state within few weeks and months with a complete retrospective changes in recovery of reference values.
The aim of this work was to evaluate a group of patients with diagnosis of ITP treated or followed from 1979 to 1999.
There were found no differences in achieving the remission in the acute phase of ITP (this means till the 6th month from the first documented thrombocytopenia) according to retrospective analysis and comparison of three groups of children in whom the diagnosis of ITP was made from 1979 to 1991 (group A), from 1992 to 1994 (group B) and from 1995 to 1999 (group C).
The groups differed in their therapeutic strategies in various time periods as to the time of the diagnosis. In group A, 75 % of patients were treated with oral corticosteroids (prednisone). In group B, 10.8 % of patients were treated with i.v. application of corticosteroids and 43.3 % had no therapy in the acute phase. In group C, 28 % of patients were treated with i.v. application of corticosteroids and 36.6 % of patients had no therapy applied. A comparable degree of remission in the acute phase with 48 %, 54 %, or 50 % of children with reference values of platelets at the time of six months from the beginning of the disease were achieved.
In the group A, the remission was achieved in 85 % of children at the end of the 5th year of the follow-up, in the group B in 75 % of children to the latest control of platelets in our outcome clinic for children and follow up in the group C in 68 % of children the remission was achieved after one year. ***(Tab. 4, Fig. 2, Ref. 10.)***
Key words: immune thrombocytopenic purpura, ITP, thrombocytopenia, children, treatment.

Immune (idiopathic) thrombocytopenic purpura (ITP) is one of the most commonly acquired bleeding disorders in children. According to the duration of thrombocytopenia, the period from the first record of thrombocytopenia till the end of the 6th month of duration is considered as the acute phase, and that following the latter is considered as the chronic phase. The period between the 6th and the 12th months of illness is also designated as an early chronic phase.

It was reported that 70 to 80 % of children go through the acute phase lasting from weeks to months with a complete recovery of reference values of platelets (3, 6, 10).

Lately, there have been some changes in therapeutic approaches in the treatment of ITP in children in acute and also in chronic phases of the disease. In all these approaches, there is one common principle — to treat the patient not the number of platelets.

In our analysis, we present the results of a retrospective analysis of a group of children (patients) with the diagnosis of ITP evaluating the long-term outcome of the illness in accordance with the changes in the therapeutic approaches.

Material and results

A group of 159 children treated and followed from 1979 till 1999 due to the diagnosis of ITP at out-patient clinic Depart-

Department of Haematology and Transfusiology of Children's University Hospital, Comenius University, Bratislava, 2nd Pediatric Clinic, Faculty of Medicine, Comenius University and Children's University Hospital, Bratislava, and Department of Children Oncology, Children's University Hospital, Bratislava

Address for correspondence: E. Hostynova, MD, Dept of haematology and transfusiology, Children's University Hospital, Limbova 1, SK-833 40 Bratislava 37, Slovakia.
Phone: +421.2.59371111

Tab. 1. Distribution of 159 children with ITP into groups A, B, C.

	A 1979-1991	B 1992-1994	C 1995-1999
Number of children (B:G)	40 (14:26)	37 (21:16)	82 (29:53)
mean age	7y	6y2m	6y11m
range (R) of age	16y1m-6m	14y4m-2m	15y3m-1m

B — boys; G — girls; R: x_{max}-x_{min}; y — years; m — months

Tab. 2. Distribution of 159 children with ITP into groups A, B, C according to the severity of thrombocytopenia.

Platelets counts ($x10^9$/L)	A		B		C	
	number	%	number	%	number	%
<10	9	22,5	16	43,3	24	29,3
11-30	8	20,0	6	16,2	17	20,7
31-50	8	20,0	3	8,1	11	13,4
51-100	4	10,0	9	24,3	16	19,5
>100	3	7,5	3	8,1	13	15,9
no defined	8	20,0	0	0	1	1,2
sum	40	100,0	37	100,0	82	100,0

ment of Haematology and Transfusiology and 2nd Pediatric Clinic of Children's University Hospital in Bratislava were evaluated according to their health care documentation. The whole group of children was divided into three groups, according to the time of diagnosis of ITP. In group A, there are 40 children (the period from 1979 to 1991). In group B, there are 37 children diagnosed from 1992 to 1994, and in group C, there are 82 children diagnosed from 1995 to 1999.

The diagnoses were established according to criteria known for the diagnosis of ITP: a) number of platelets <150x10^9/L, b) clinical signs of haemorrhagic diathesis whether cutaneous or mucous, c) no other cause of thrombocytopenia identified, d) evaluation of peripheral blood film without any numerous signs of cytomorphological pathology, e) evaluation of bone marrow smears if necessary (3).

Number, sex and age of patients in individual groups are shown in Table 1. Out of all 159 children, there were 64 boys (40.2 %) and 95 girls (59.8 %), 1:1.5 boys to girls. The mean age of children at the time of diagnosis in all three groups was seemingly the same, with a broad span.

The division according to the number of platelets at the time of the first record of thrombocytopenia is shown in Table 2. In group A (diagnosis established from 1979 to 1991) in about one fifth of patients (8 patients) it was not possible to document the first count of platelets at the diagnosis. Out of the rest of this group (32 children), in more than of one half of patients the count of platelets was lower than 30x10^9/L (17 from 32 children). Similar figures were found in group B and as well as in group C of patients. An important finding in group C is that the platelet count was higher than >51x10^9/L in one third of patients with thrombocytopenia.

Tab. 3. Distribution of 159 children with ITP according to the initial therapy into groups A, B, C.

Initial therapy	A (n=40)		B (n=37)		C (n=82)	
	number	%	number	%	number	%
prednisone	30	75,0	2	5,4	6	7,3
I.v. corticotherapy	5	12,5	4	10,8	23	28,0
No therapy	5	12,5	16	43,3	30	36,6
I.v. Ig	-	-	1	2,7	3	3,7
splenectomy (SE)	-	-	-	-	1	1,2
combination of therapy*	-	-	14	37,8	19	23,2

*metylprednisolone+prednisone (B1x, C5x)
metylprednisolone+dexamethasone+SE (C1x)
metylprednisolone+prednisone+IVIG+SE (C1x)
metylprednisolone+prednisone+IVIG (B1x, C5x)
metylprednisolone+prednisone+SE (B1x)
metylprednisolone+IVIG (B3x, C2x)
metylprednisolone+SE (B2x)
metylprednisolone+IVIG+SE (B3x)
only hydrocortisone (C1x)
prednisone+IVIG (C3x)
prednisone+IVIG+SE (C1x)
prednisone+SE (B2x)
prednisone+metylprednisolone+IVIG+azathioprine+cyclosporin+SE (B1x)

In the initial phase of the illness, a different treatments in various periods of time were applied in our groups of patients. Table 3 shows various therapeutical approaches in the initial treatment of ITP applied in different departments within Slovakia.

There was a larger group of children in group B and C with combination of immunosuppressive therapy or combined with surgical therapy. These are patients in the initial phase, mostly treated in other hospitals in Slovakia, with various combinations of treatment (shown in Table 3) and due to of unsatisfactory response to therapy (as to speed of answer to treatment or to level of thrombocytopenia) they were admitted to our hospital. Due to a small number of children and a huge variety of combinations of therapy as well as to no knowledge about criteria for individual combinations in therapy, it was not possible to evaluate these combinations of therapy systematically according to its effect.

From the point of evaluation and transition of illness to the chronic form, is important to decrease the count of platelets at the time of six months of the first documented decreased level of platelets. Such evaluation is done in our groups of patients (A, B, C) in Figure 1.

Although there was a change in the therapeutical approach in the diagnosis of ITP (Table 3, groups B and C), and although there was a greater part of children with lower initial number of platelets in these groups of patients (Table 2), no basic differences were found in the number of children achieving the remission of thrombocytopenia within a 6-month period subsequent to the statement of diagnosis. A stable number of platelets over the level of 150x10^9/L was achieved in 19 out of 40 children in group A of patients (47.5 %); in group B in 20 out of 37 children (54.1 %) and in group C in 41 out of 82 children (50.0 %).

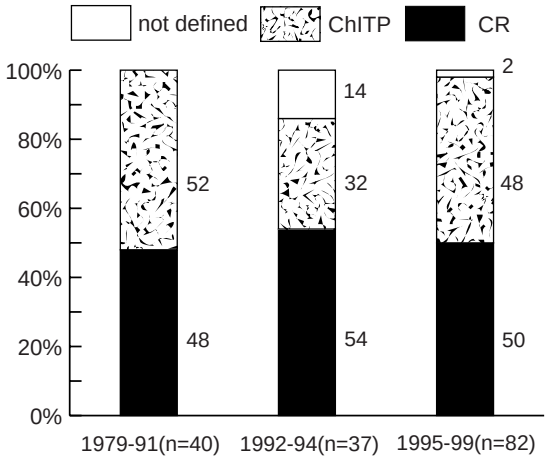

Fig. 2. Distribution 159 children with ITP according to actual condition of illness to the given time in groups A, B, C. ChITP — chronic ITP, CR — complete remission

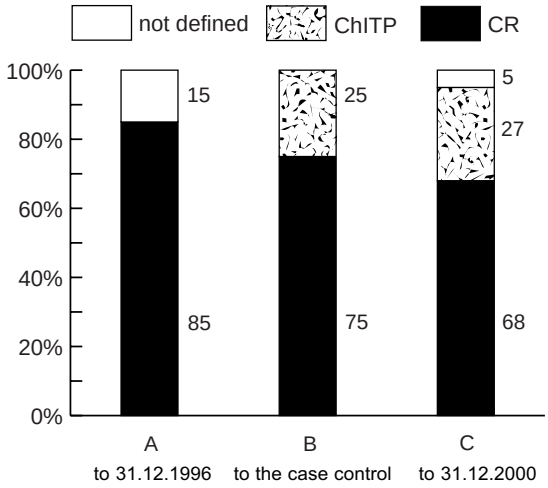

Fig. 2. Distribution 159 children with ITP according to actual condition of illness to the given time in groups A, B, C.

In the further development of the disease according to achievement of remission of the disease in a long-term follow-up, we tried to evaluate the defined time (5 years). For instance, in group A as to the December 31, 1996.

In group B, the evaluation after 5 years was modified for the latest documented control in an out-patient clinic of our department and the results as to this time. This was necessary because more than a half of patients interrupted their visits in our hospital after achieving the remission before the December 31, 1999, and this could influence the rate of remissions in this group very significantly. Children in group C were evaluated as to the time of the December 31, 2000 (it means one year after the last patient in this group could have been diagnosed). The results are presented in Figure 2.

Despite the discrepancies in time criteria, we have found that the rate of remission in our group of patients corresponds with the data in literature. In group A, where the main treatment approach resides in the use of Prednison, the remission was achieved in 34 out of 40 children (85 %). In group B, as to the time of the last control at our out-patient clinic, 28 out of 37 children were in remission (75.7 %), and in group C, after one-year follow-up, there out of 56 of 82 children were in remission (68.3 %).

According to the severity of thrombocytopenia in 37 children (23.3 %) with chronic ITP out of the whole group of 159 children, as at given time 25 of 159 (15.7 %) were over the critical "bleeding" level with >50x10^9/L platelets. 10 children (6.3 % out of 159 children) had 31—50x10^9/L platelets; only 2 children out of 159, as to the given time, had platelets below 30x10^9/L. These data are presented in Table 4.

The reason for the differences in achieving the remission in individual groups resides probably in the duration of the follow-up. In group A, it was 64 months (the follow-up lasted 5 years). In group B, the mean time to achieve the remission was 16.2 months (followed till the last control at out-patient clinic). In group C the shortest the mean time was, namely 7.3 months (following 12 months after the last ITP was diagnosed).

Splenectomy is another approach in the treatment of ITP, that should be very thoroughly considered, especially in children. This procedure was done in 22 patients (13.8 %) with chronic ITP out of the whole group of 159 children. In group A, 7 out of 10 children achieved complete remission of ITP after splenectomy, in group B, 6 out of 8 children achieved remission, and in the last group C, 3 children out of 4 achieved the remission. These results are comparable with literature data, where 16 children out of 22 achieved remission of thrombocytopenia after splenectomy, thus forming 72.7 % (8).

Any of children had any serious bleeding complications, for instance bleeding to the central nervous system (CNS). Mostly cutaneous and mucous haemorrhagic signs were seen. Only in one case the splenectomy was indicated as a vital indication, namely, because of metrorrhagy that not responded to medications and the supportive therapy.

Tab. 4. Distribution of 159 children with ITP into groups A, B, C and according to the severity of thrombocytopenia at the given time.

Platelets counts (x10^9/L)	A (to the December 31, 1996)		B (to the date of last control)		C (to the December 31, 2001)	
	number	%	number	%	number	%
<30	-	-	1	2,7	1	1,2
31-50	6	15,0	1	2,7	3	3,7
51-100	-	-	7	18,9	5	6,1
101-150	-	-	-	-	13	15,9
>151	34	85,0	28	75,7	56	68,3
not defined	-	-	-	-	4	4,9
sum	40	100,0	37	100,0	82	100,0

Discussion

In general, immune (idiopathic) thrombocytopenic purpura in children is a benign disease. Serious bleeding symptoms, for

instance intracranial bleeding to CNS is documented in about 1% of all cases of severe thrombocytopenia, mainly by platelets level of 10 to 20x10^9/L (2). The disease appears in predominantly healthy children, mainly at the age from 4 to 8 years of life, with no predominance in sex, however in connection with previous acute infection, mainly that of upper respiratory tract (5). Children suffering from immune thrombocytopenia achieve the remission of disease in 70 to 80 %, often in very short time after being diagnosed (1, 4). This knowledge corresponds with the results in our group of patients. The division into three groups in our study was the first of all time criteria (time of diagnosis, time of duration of the disease before evaluation), as well as the comparison of various therapeutic approaches in the initial phase of the disease. Group A represents children 75 % of whom were treated in the initial phase with oral corticosteroid — prednisone. In group B 43.3 % of children were not treated with medicaments. In this groups the approach "wait and see" was chosen; as well as in 36.6 % of children in group C (Tab. 3). In all three groups, a relatively high number of children who achieved remission was found, i.e. the level of platelets over 150x10^9/L, in 6 month after the first records of thrombocytopenia (48 %; 54 % respectively 68 %) (Fig. 1).

Alike in the chronic form of thrombocytopenia with moderate thrombocytopenia it is not recommended to treat the count of platelets, but to follow up and treat the patient. On the base of clinical experience and evaluation of large groups of patients, it was found out that at the level of >50x10^9/L platelets, no spontaneous bleeding signs are seen; at the count of platelets between 10 to 50x10^9/L the haemorrhagic signs could rise spontaneously, adolescent girls could display hypermenorrhagy. From the point of view of haemorrhagic signs the levels of 10x10^9/L and less are critical and need medicamentous and supportive treatment (5), according to other authors these critical levels are already of 20x10^9/L or less (1). These limits of platelets levels lead to various approaches in chronic forms of ITP, the treatment is reserved for patients with very low platelets counts and bleeding signs, mostly those of mucous haemorrhagic diathesis (1).

In our long term follow-up of 159 children 41 of them (26 %) had platelets less than 150x10^9/L. Only two of them at the time of evaluation had less than 30x10^9/L, 10 children had their platelets in the range between 30 to 50x10^9/L, and 25 children had platelets over 50x10^9/L.

Naturally the choice of treatment and its intensity also in these cases require an individual approach with respect to the clinical signs of haemorrhagic diathesis. Also in chronic forms of ITP it is necessary to consider the principle that the patients should be treated not his platelet count. All combinations of medicamentous therapy in the acute phase or long-term follow-up without therapy leads to high rate of remission of ITP; it has been described, that only about 24 % of children suffer with chronic form of ITP for a long time (4). It is not clear, whether in patients showing reference levels of platelets was this the "real respond" to the medicamentous treatment, or the remission took place due to spontaneous gradually reconstitution (7).

On the base of literature data and evaluation of our group of patients it can be stated, that immune (idiopathic) thrombocytopenic purpura is a common benign disease requiring strong individual approach to the treatment, considering not only the platelet count, but also the clinical symptoms of the patient (9). In the acute phase, alike in the chronic phase of the disease, also negative aspects of other immunosuppressive treatments should be considered. This treatment should be reserved for patients with thrombocytopenia and with cutaneous and mucous haemorrhagic diathesis or for patients with thrombocytopenia and acute infection. Children with thrombocytopenia with only discrete cutaneous haemorrhagic disease should not be treated; should be admitted to hospital and observed until the haemorrhagic signs disappear. In taking care of a child with thrombocytopenia a part of responsibility should be beared not only by the doctor but also by the parents who can help with their part of responsibility in taking care of the child in order to minimalize a possibly unnecessary immunosuppressive treatment with its negative consequences.

References

1. Blanchette V, Freedman J, Garvey B. Management of chronic immune thrombocytopenic purpura in children and adults. Semin Hematol 1998; 36 (Suppl 1): 36—51.

2. Gaedicke G. Childhood autoimmune thrombocytopenia : to treat or not to treat. In: Sutor T (Ed). Thrombocytopenia in Childhood. Stuttgart—New York, Schattauer 1994, p. 129—139.

3. George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, Blanchette VS, Bussel JB, Cines DB, Kelton JG, Lichtin AE, McMillan R, Okerbloom, JA, Regan DH, Warrier I. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood 1996; 88 (1): 3—40.

4. George JN, Raskob E. Idiopathic thrombocytopenic purpura: a concise summary of the pathophysiology and diagnosis in children and adults. Semin Hematol 1998; 35 (Suppl 1): 5—8.

5. Imbach P. Immune thrombocytopenia in children: the immune character of destructive thrombocytopenia and the treatment of bleeding. Semin Thromb Hemostasis 1995; 21 (3): 305—312.

6. Kuhne T, Imbach P. Management of children with acute and chronic immune thrombocytopenic purpura. Transfus Sci 1998; 19 (3): 261—268.

7. Lilleyman JS. The therapeutic challenge of chronic severe ITP in children. In: Sutor T (Ed). Thrombocytopenia in Childhood. Stuttgart—New York, Schattauer 1994, p. 141—148.

8. Mantadakis E, Buchanan GR. Elective splenectomy in children with idiopathic thrombocytopenic purpura. J Pediat Hematol Oncol 2000; 22 (2): 148—153.

9. Medeiros D, Buchannan GR. Idiopathic thrombocytopenic purpura: beyond consensus. Cur Opin Pediat 2000; 12 (1): 4—9.

10. Nugent DJ. Immune thrombocytopenic purpura: Why treat? J Pediat 1999; 134: 3—4.

Received February 10, 2002.
Accepted March 12, 2002.