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INTERFERON – ALPHA THERAPY FOR REFRACTORY IDIOPATHIC THROMBOCYTOPENIC PURPURA IN CHILDREN*

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SUMMARY: Yeşilipek MA, Yeğin O. (Hematology Unit, Department of Pediatrics, Akdeniz University Faculty of Medicine, Antalya, Turkey). Interferon-alpha therapy for refractory idiopathic thrombocytopenic purpura in children. Turk J Pediatr 1997; 39: 173-176.

Interferon (IFN)-alpha therapy was presented as a possible treatment for refractory immune thrombocytopenic purpura (ITP). We used 3 x 10^6 U recombinant IFN alpha, subcutaneously three times a week, every other day, for a total of 12 doses, in five children with refractory ITP. Three patients showed no response and were classified with Type III. One patient gave a partial response, and the other one had been in remission for 71 weeks as of this writing. This is the longest remission period reported for IFN therapy. The patients were classified Types IIb and I, respectively. The therapy was well tolerated. We conclude that further studies are to needed evaluate IFN-alpha therapy in childhood ITP. *Key words: interferon alpha, immune thrombocytopenic purpura, childhood.*

Acute idiopathic thrombocytopenic purpura (ITP) represents the most frequent hemorrhagic diathesis in childhood. ITP is an acquired thrombocytopenia accompanied by reduced platelet survival which is caused by premature degradation of the platelets by the reticuloendothelial cell system of the spleen or liver. The incidence of ITP is approximately one per 10,000 children. When the condition persists (about 10% of cases), with or without therapy, for more than six months, traditionally it is referred to as chronic ITP. It is well known that the risk of intracranial hemorrhage (ICH) is higher in chronic patients. The incidence of ICH increases with the passage of time, starting at 0.3 percent immediately after diagnosis, and increasing to two percent at 24 months[1].

Sometimes the management of chronic or refractory patients may fail with conventional regimens (steroids, immuneglobulins, splenectomy, ascorbic acid, mega-dose methylprednisolone, Anti-D, etc.) and may cause a clinical problem.

We studied the effect of IFN-alpha on children with refractory ITP who had failed to improve with conventional therapies.

Material and Methods

We used IFN-alpha in five children who had no response to previous ITP treatment modalities. The cases are summarized in Table I. All of the patients had the symptoms of petechiae, ecchymoses and epistaxis. Case 5 also had

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menorrhagia. Thrombocytopenia associated with increased immature megakaryocytes and absence of malign cells in the bone marrow were accepted as the criteria for the diagnosis of ITP. None of the patients had clinical or laboratory evidence of cytomegalovirus, Ebstein Barr virus, Hepatitis B virus infection or systemic lupus erythematosis. The treatment course consisted of 12 injections of 3 x 10^6 U recombinant IFN-alpha (IFN-alpha 2a for Cases 1, 4 and IFN alpha 2b for Cases 2, 3, 5) given subcutaneously three times a week, every other day. The responses are shown in Table II. We classified the responses according to a scale that has previously been described[2]. Type I indicates a complete response, with a return of the platelet count to greater than 200 x 10^9/L for longer than three months. Type IIa indicates a partial response with a platelet count of 30 to 200 x 10^9/L for longer than six weeks; Type IIb represents a partial response with platelets of 30 to 200 x 10^9/L for less than six weeks; Type III means no response with a static platelet count; and Type IV indicates worsening of the platelet count, with an increased clinical bleeding tendency.

Table I: Clinical Characteristics of the Patients

Patient	Sex	Age (yrs)	Time from Diagnosis to IFN Therapy (Months)	Previous Treatments (*)
1	M	13	30	P, D, G, M, S
2	M	2	8	P, G, M, Vit C
3	F	3.5	13	P, G, M
4	F	7	31	P, G, M, Vit C
5	F	15	22	P, G, M

(*) P: Prednisolone, D: Danazol, G: Gammaglobulin,
M: High-dose methylprednisolone, S: Splenectomy.

Table II: Response to IFN Treatment

Patient	Maximum PLT* Count (x10^9/L)			Time to Max Response (days)	Duration of Response (weeks)	Last PLT* Count (x10^9/L)	Response Type
	Pre IFN	During	Post				
1	8	64	500	21	71	250	I
2	9	150	57	–	–	57	IIb
3	19	29	28	–	–	25	III
4	46	64	60	–	–	60	III
5	6	16	19	–	–	15	III

* PLT: Platelet.

Results

The therapies were well tolerated. No response was detected during treatment in the first patient, except a rise on the fourth day of treatment for three days; however, after 21 days the patient's platelet count increased to 380 x 10^9/L, and he had been in remission for 71 weeks as of this writing. Case 2, whose response was classified as IIb, showed an increase in the platelet count after the third dose of IFN (9 to 150 x 10^9/L), but it decreased three days later. The Cases 3 and 4 showed minimal and Case 5 no response; thus the last three patients were classified as type III.

Discussion

Conventional therapies may fail in some children with immune thrombocytopenic purpura, (ITP). Because of the life-threatening risk of bleeding, new therapeutic agents are being investigated. Some authors have reported that (IFN-alpha) therapy may lead to remission in some, but not all, of these chronic or refractory patients[3-6].

Proctor et al.[6] demonstrated that short-course, low-dose IFN-alpha was useful in some cases of severe steroid-non-responsive ITP in adult patients. However, Hurtado et al.[5] reported that neither platelet count nor bleeding manifestations improved with IFN. A few studies have been reported in childhood, but there is still controversy over the use of IFN-alpha therapy in ITP.

Our first patient experienced an increase in the platelet count after therapy was completed. This finding is in contrast with previous reports in children, as platelet counts usually rise during the treatment[4]. The patient was still in remission after 71 weeks, as of this writing, which is the longest reported period in the literature for IFN-alpha therapy in chronic ITP. Spontaneous remission is another possibility that must be kept in mind in these patients.

The mechanism of action of IFN in ITP is unclear. There is evidence as to inhibitory effect of IFN on B-cell immunglobulin production[4]. The correlation between the low serum levels of IgG and PAIgG and increased platelet counts confirms this suggestion[7]. Hurtado et al.[5] found that IFN stimulates natural killer activity. Because these cells are responsible for antibody-dependent cell-mediated cytotoxicity, they suggested that it is probably the cause of lack of response.

Ishii et al.[8] administered six million units of IFN-alpha and compared the improved response rate to previous studies using three million units. No difference was found, and the authors concluded that a dose of six million units may be too large to treat some ITP patients.

In conclusion, IFN therapy may be one treatment choice for patients with refractory ITP because of its having fewer side effects and being safe for viral transmission. However, this therapy is still controversial, and the results vary

from center to center. Large collaborative trials in refractory patients are needed in order to clarify the treatment protocols and the possible value of IFN-alpha therapy in these special patients.

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