Therapeutic Experience on 934 Adults With Idiopathic Thrombocytopenic Purpura: Multicentric Trial of the Cooperative Latin American Group on Hemostasis and Thrombosis

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In order to analyze the usefulness of different types of treatment in relation to the interval since the onset of idiopathic thrombocytopenic purpura (ITP), a collaborative study of 934 adult patients was undertaken. Prednisone was administered to 818 patients, and 32% of them achieved prolonged complete remission (PCR). However, only 14% of patients who had ITP for more than six months achieved a prednisone-induced PCR ($P < .01$). Splenectomy was done in 399 patients, and 65% of them achieved PCR; the remission rate did not vary with the interval since the onset of ITP. Of 120 patients with chronic ITP that was refractory to corticosteroids and splenectomy, 91 received either azathioprine or cyclophosphamide; 21% of them achieved PCR and 55% had a favorable response. None of 19 patients treated with vincristine and only one of ten patients treated with vinblastine-loaded platelets achieved PCR.

IDIOPATHIC thrombocytopenic purpura (ITP) is an immune disease that is characterized by destruction of opsonized platelets by the reticuloendothelial system. The majority of patients with ITP respond to treatment with corticosteroids or to splenectomy.[1-7] In recent years, immunosuppressive agents, as well as other forms of therapy, have also been used in patients with ITP, particularly severely ill chronic patients.[1-5,8-15]

This article describes the results of therapy in 934 adult patients with ITP. These patients were seen by members of the Cooperative Latin American Group on Hemostasis and Thrombosis (CLAHT group), who used precise and uniform criteria in their evaluation.

MATERIALS AND METHODS

All patients were more than 16 years of age at the time of study. The 934 cases were seen in ten different hospitals (Table 1). There were 719 women (77%), aged 16 to 87 years, and 215 men (23%), aged 20 to 65 years. The onset of ITP occurred between the ages of 10 and 87 years, but was noted predominantly in patients less than 40 years of age (687 cases, 74%). The criteria used for the diagnosis of ITP were thrombocytopenia lasting two weeks or more in conjunction with a normal white count and no anemia except when there was a positive Coombs' test (eight patients, 0.8%), or active bleeding, increased numbers of megakaryocytes in the bone marrow, a nonpalpable spleen, no recent ingestion of drugs that could be implicated, and no alternative explanation for the thrombocytopenia (such as systemic lupus erythematosus or consumption of platelets in a clotting process).[1-6,16] Fifty-five percent of 211 cases showed positive results for antiplatelet antibodies when tested using various techniques.[1-5]

The patients were arbitrarily defined as acute, subacute, or chronic, based on the amount of time between the onset of the disease and first treatment: acute ITP, less than two months; subacute ITP, two to six months; and chronic ITP, greater than six months.

The criteria for response to treatment have been previously reported[5,14] and were prolonged complete remission (PCR), which was considered to be a normal platelet count six months after all treatment was discontinued; complete remission with relapse, which was normalization of the platelet count followed by reappearance of thrombocytopenia three or more months after all treatment was stopped; partial remission, which was symptomatic improvement with a platelet increase greater than 50,000/μL but less than normal for a period lasting at least three months during or after treatment (splenectomy or steroidal and nonsteroidal immunosuppressive therapy); and no response, which was persistent clinical symptoms with a platelet count less than 50,000/μL. Prolonged complete remission, complete remission with relapse, or partial remission were considered to be favorable responses. Spontaneous remission was considered to have occurred when PCR was seen more than eight weeks after any previous treatment.

Therapeutic Program

The therapeutic program involved treatment with the following techniques.

Corticosteroids. Prednisone or its equivalent of another corticosteroid was given at a daily dosage of 1 to 3 mg/kg during the first two to four weeks; the maintenance dosage was 0.3 to 1 mg/kg daily or at intermittent intervals if the treatment was for more than 90 days. Only patients who received corticosteroids for at least 30 days were evaluated.

Splenectomy. Surgery was performed on patients who failed to develop a PCR with corticosteroids or immunosuppressants.

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Table 1. Multicentric Latin American Study of 934 Adults With Idiopathic Thrombocytopenic Purpura

Authors and Institution	Country	No. of Cases
Pizzuto and Ambriz, Instituto Mexicano del Seguro Social, Mexico City	Mexico	225
Campuzano and Restrepo, Universidad de Antioquia, Medellin	Colombia	166
Larrain et al, Universidad de Chile, Santiago	Chile	146
Romero et al, Instituto Mexicano del Seguro Social, Guadalajara, Jalisco	Mexico	107
Gonzalez et al, Secretaria de Salubridad y Asistencia Publica, Mexico City	Mexico	65
Hendler et al, Osplan, Buenos Aires	Argentina	57
Elizondo et al, Hospital San Juan de Dios, San Jose	Costa Rica	52
Rico et al, Instituto Mexicano del Seguro Social, Monterrey, N.L.	Mexico	51
Sanchez-Avalos et al, Universidad de Buenos Aires, Buenos Aires	Argentina	35
Almagro and Espinoza, Instituto de Hematologia, La Habana	Cuba	30
Total Number of Cases		934

Selected patients on whom splenectomy was performed as the first therapeutic approach were also evaluated (25 cases).

Immunosuppressive agents. Immunosuppressive medications were used in patients with chronic ITP who did not achieve PCR with the use of corticosteroids or splenectomy. We evaluated only those patients who received cyclophosphamide or azathioprine for a minimum of 16 weeks[5,14] at a daily dosage of 1 to 2 mg/kg.

Other treatments. Vincristine was given intravenously at a dosage of 1 to 2 mg every one or two weeks for a minimum of four doses[15]; vinblastine-loaded platelets were administered according to the method of Ahn[8] for up to four doses intravenously. This latter treatment was used on only a small group of patients with chronic ITP who had repeated episodes of bleeding and who were refractory to all previous treatments, including corticosteroids, splenectomy, and immunosuppressants.

RESULTS

Of the 934 patients studied, nine patients with acute ITP (0.9%) did not receive any treatment because they had spontaneous remissions. Of the 925 remaining cases, the best therapeutic responses were observed in patients treated with corticosteroids or splenectomy or both (Table 2): an excellent response (prolonged complete remission) was achieved in 521 patients (56%) receiving either or both types of treatment, while 336 patients (36%) achieved a fair response (remission with relapse and partial remission). Of those patients who were refractory to both corticosteroids and splenectomy, an additional 55% (50 of 91 patients) responded favorably to either azathioprine or cyclophosphamide (Table 2).

Therapeutic Response

Corticosteroids. The relative effect of corticosteroids on acute, subacute, and chronic ITP was evaluated in 373 patients. Table 3 shows that a prolonged complete remission was observed in only 14% of the cases with chronic ITP compared with a 39% response rate in ITP cases treated within six months of onset ($P < .01$). The response rates in patients with acute and subacute ITP were similar (40% *v* 35%). Of 477 cases evaluated, the duration of corticosteroid therapy did not affect the therapeutic response. Indeed, the use of corticosteroids for more than 30 to 45 days demonstrated no additional favorable results (Table 4).

Splenectomy. The responses obtained with splenectomy were better than those with either corticosteroids or other forms of treatment (Tables 2 and 3); of 399 patients who had their spleens removed, 259 (65%) achieved PCR and 325 (81%) had a favorable response. Moreover, in contrast to corticosteroid therapy, the favorable results did not diminish with the increased interval since onset of ITP (Table 3). In addition, when splenectomy was the initial therapeutic approach in a group of 25 patients with chronic ITP, the favorable results (PCR) in 17 out of 25 cases (68%) were no

Table 2. Total Response to the Different Treatments Used in Adults With Idiopathic Thrombocytopenic Purpura

Treatment	No. of Cases	Prolonged Complete Remission	Complete Remission With Relapse	Partial Remission	Favorable Response	Failure
Corticosteroids	818*	262 (32%)†	124 (15.0%)	146 (18.0%)	532 (65%)	286 (35%)
Splenectomy	399‡	259 (65%)§	41 (10.0%)	25 (6.0%)	325 (81%)	74 (19%)
Subtotal	925‖	521 (56%)				
Immunosuppressants						
Cyclophosphamide	50¶	11 (22%)	6 (12.0%)	12 (24.0%)	29 (58%)	21 (42%)
Azathioprine	41¶	8 (19%)	4 (10.0%)	9 (22.0%)	21 (51%)	20 (49%)
Subtotal	91¶	19 (21%)				
Other Treatments						
Vincristine	19¶		2 (10.5%)	2 (10.5%)	4 (21%)	15 (79%)
Vinblastine-loaded platelets	10#	1 (10%)	2	3	6	4
Subtotal	29					
Total	925‖	541 (58%)				

*In the participating groups the initial complete response varied from 58% to 71% encountered while the steroid was still being given.

†In the participating groups the total response varied from 12% to 42%.

‡In the participating groups the initial complete response varied from 69% to 95% until three months after splenectomy.

§In the participating groups the total response varied from 46% to 84%.

‖Nine patients with acute ITP obtained spontaneous remission, therefore they did not receive any treatment.

¶All cases had been treated with corticosteroids and splenectomy.

#All patients had been treated with immunosuppressive agents.

Table 3. Incidence of Prolonged Complete Remission (PCR) and Duration of Idiopathic Thrombocytopenic Purpura in 373 Patients

Treatments	Acute ITP			Subacute ITP			ITP Less Than 6 Months in Duration			Chronic ITP		
	No. of Cases	No. With PCR	Incidence (%)	No. of Cases	No. With PCR	Incidence (%)	No. of Cases	No. With PCR	Incidence (%)	No. of Cases	No. With PCR	Incidence (%)
Corticosteroids	184	74	40	57	20	35	241	94	39	132	19	14
			P = NS						$P < .01$			
Splenectomy	28	17	61	15	10	66	43	27	63	171	91	53
			P = NS						P = NS			
Other treatments*										120	19	16

*Cyclophosphamide, azathioprine, vincristine, or vinblastine-loaded platelets.

†Without treatment.

‡After eight weeks of steroids (five cases) or steroids and splenectomy (eight cases).

§In nine cases the spontaneous remission appeared ten to 52 months after discontinuing the last treatment (corticosteroids, splenectomy, or immunosuppressive agents); in the other five patients, two to six months after steroids and splenectomy.

‖This percentage increases up to 6.8% if the 27 cases with spontaneous remission after failure of different treatments are compared with the 393 patients who did not show a prolonged complete remission.

different from those obtained in other cases when splenectomy was a second treatment (Tables 2 and 3).

Immunosuppressive agents and other treatments. Ninety-one patients refractory to corticosteroids and splenectomy were treated with either cyclophosphamide or azathioprine. Of these, 21% achieved PCR and 55% obtained a favorable response (Table 2). Of 19 patients treated with vincristine or vinblastine-loaded platelets, only four had a favorable response (21%) and only one developed PCR (Table 2).

Complications of treatment. As shown in Table 5, the primary complications observed were the common ones for those treatments. These complications increased with the use of more aggressive therapeutic resources. The only patient registered with a neoplasm (endometrial carcinoma) received treatment with cyclophosphamide for 22 weeks.

Mortality. Of 934 patients, 47 (5%) died; 27 had acute or subacute ITP and 20 had chronic ITP. The cause of death was cerebral hemorrhage in 27 patients, pulmonary or gastrointestinal bleeding in nine patients, massive purpura in ten patients, and in one case, fatal sepsis after splenectomy.

DISCUSSION

Although this report has the drawbacks of a multicentric retrospective study and many of the points that were made are not entirely new, they were obtained from a consistent series of patients. We were able to analyze the response of a large group of patients with ITP who were treated at varying times during the evolution of their disease using criteria that were more rigid than usual. For example, other investigators have included children and adults in their study groups,[1-6] while only adults were studied in ours. Moreover, PCR was defined in a more precise manner so that transitory responses that simulated a complete remission were clearly eliminated. Based on these observations, the

Table 4. Duration of Corticosteroid Therapy and Incidence of Prolonged Complete Remission (PCR) in Adults With Idiopathic Thrombocytopenic Purpura

Duration (d)	No. of Cases Treated	PCR	P Value
30-45	231	73 (32.0%)	NS
46-90	51	16 (31.0%)	
>90	195	58 (30.0%)	NS
Totals	477	147 (30.8%)	

Table 5. Complications of Treatment

Complication	Total No. of Patients	No. of Patients With Complications	Percentage
Steroids	818		
Acne		123	15
Gastritis		55	7
Diabetes mellitus		24	3
Psychosis		4	0.4
Infections		44	5*
Splenectomy	399		
Subphrenic abcess		10	2.5
Pneumonia		6	1.5
Thromboembolism		6	1.5
Visceral lesions		4	1
Bleeding		4	1
Death		1	0.2†
Azathioprine and cyclophosphamide	91		
Leucopenia		27	30‡
Infections		9	10*
Hemorrhagic cistitis		2	2§
Neoplasms		1	1‖
Vincristine	19		
Neuropathy		6	32
Vinblastine-loaded platelets	10		
Fever and arthralgias		7	70
Increased of purpura		2	20
Neuropathy and agranulocytosis		1	10¶

*Genital or urinary infections in most cases.

†Sepsis in early postoperative period.

‡Not less than 10^9/L of granulocytes.

§With cyclophosphamide.

‖Endometrial carcinoma.

¶With the third treatment.

effect of corticosteroids, splenectomy, and immunosuppressants could be compared in a large sample of adults with acute, subacute, or chronic ITP with a high degree of reliability in the results.

The responses to corticosteroids and splenectomy achieved in this study are similar to those previously reported.[1-7] These two forms of therapy proved to be the most efficient because the majority of adult patients with ITP obtained some type of favorable response to both forms of therapy. The best results with corticosteroids were obtained in patients with ITP of less than six months' duration (39% PCR), while PCR was noted in only 14% of patients with chronic ITP (Table 3). Consequently, we recommend corticosteroids as the initial treatment of choice, particularly in cases of acute or subacute ITP where the PCR rate is high. Moreover, the prolonged administration of corticosteroids is not recommended, because a favorable response, when it occurs, appears rapidly in one or two weeks.[3,5] This recommendation is supported by the data on 477 patients analyzed in this report, which show that continuation of corticosteroids for more than 45 days does not produce an increased incidence of PCR and only increases the possibility of undesirable side effects.[2,5,7] The use of corticosteroids in patients with chronic ITP, where the PCR rate is low, seems most effective as a symptomatic and transitory approach to the treatment of either hemorrhagic episodes or as part of the preparatory program for splenectomy. Prolonged treatments with corticosteroids under these conditions should be avoided.

As shown in this report and by other investigators,[1-7] splenectomy is the most successful therapeutic approach in ITP because it produced the highest rate of PCR (65% of 399 patients). The beneficial effects of splenectomy, unlike those of corticosteroids, are unaffected by the interval between the onset of the disease and treatment. Nevertheless, because major surgery is involved, it has usually been considered as the treatment of second choice following a demonstrated lack of response to corticosteroids. From the present experience, however, this viewpoint seems valid only for adults with acute or subacute ITP and less so for patients with chronic ITP where the response to corticosteroids is poor[1-3,5,6] and always much worse than that obtained with splenectomy (Tables 2 and 3). Therefore, it seems rational to propose splenectomy as the initial or early treatment of choice in adults with chronic ITP,[2,5,6] because the use of corticosteroids, expecially for prolonged periods, results in lost time and increases the risks unnecessarily.

Immunosuppressive agents and the other therapeutic resources employed in this study should be reserved for those patients with chronic ITP who are refractory to corticosteroids or splenectomy or both[1-15] and who have severe thrombocytopenia with repeated bleeding episodes. There are patients with ITP who, after entering the chronic stage of their illness, seem to have a decrease in the frequency and severity of their bleeding episodes.[5,17] In addition, a spontaneous increase in the platelet count to either "safe levels" or a complete remission of the ITP may appear in some patients earlier or later in the course of the disease.[5,17] In Table 6 it can be seen that a spontaneous remission occurred in up to 6.8% of the patients.

The effect of azathioprine and cyclophosphamide therapy was evaluated in 91 refractory ITP patients. Significant improvement was noted in 55% and PCR in 21%. The response to these two agents was similar and the incidence of PCR with cyclosphosphamide was considerably less than that previously reported in another large series.[14] The reason for this difference is not known. From our data, it is apparent that azathioprine and cyclophosphamide are of equal value as immunosuppressive agents. In addition, our results in the use of either vincristine or vinblastine-loaded platelets was much less encouraging than that reported in previous studies[8,15]; of 19 patients treated with vincristine, PCR was not noted and only 21% achieved favorable responses. Similarly, in ten patients treated with vinblastine-loaded platelets, only a single PCR occurred, although six of the ten patients achieved

Table 6. Incidence of Spontaneous Remission in Adults With Idiopathic Thrombocytopenic Purpura (ITP)

CLAHT Authors	Total No. of Cases	Spontaneous Remission in ITP			Total No. of Remissions
		Acute	Subacute	Chronic	
Pizzuto and Ambriz	225	4	5	9	18 (8.0%)
Campuzano and Restrepo	166*	—	—	—	—
Larrain et al	146	2	0	3	5 (3.4%)
Romero et al	107	1	0	0	1 (0.9%)
Gonzalez et al	65*	—	—	—	—
Hendler et al	57	1	2	0	3 (5.2%)
Elizondo et al	52*	—	—	—	—
Rico et al	51	0	1	1	2 (3.9%)
Sanchez-Avalos et al	35*	—	—	—	—
Almagro and Espinoza	30	1	5	1	7 (23.3%)
Total	934	9†	13‡	14§	36 (3.8%)‖

*Specific information not available.

†Without treatment.

‡After eight weeks of steroids (five cases) or steroids and splenectomy (eight cases).

§In nine cases the spontaneous remission appeared ten to 52 months after discontinuing the last treatment (corticosteroids, splenectomy, or immunosuppressive agents); in the other five patients, two to six months after steroids and splenectomy.

‖This percentage increases up to 6.8% if the 27 cases with spontaneous remission after failure of different treatments are compared with the 393 patients who did not show a prolonged complete remission.

favorable responses. It is possible that these poor results may be the result of the sequence of choices of treatment, because those patients perhaps had the most resistant disease of all. In addition, the greatest likelihood of alloimmunization to platelets may be related to those patients with the poorest response to vinblastine-loaded platelets, since the alloantibody is dominant in destruction of the loaded platelets, and the macrophages are not as important as in the case of alloantibody-mediated destruction.

In summary, we recommend corticosteroids as the initial treatment in adult cases of acute or subacute ITP; if there is not a favorable response, splenectomy must be performed. In contrast, splenectomy may be used as the initial or early treatment of choice in the chronic cases, since the use of corticosteroids, especially for prolonged periods, results in lost time and increases the risks unnecessarily. The use of more aggressive treatments is indicated only as last choice therapy for the few patients with chronic ITP who have had repeated bleeding episodes and who are refractory to corticosteroids and splenectomy. Otherwise, it would seem that conservative management is the most commendable, especially since spontaneous remission may occur more frequently than expected.

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