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Immunosuppressive Agents in the Treatment of Chronic Idiopathic Thrombocytopenic Purpura*

by

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Acute idiopathic thrombocytopenic purpura (I.T.P.) in childhood is a condition with a self-limiting course that will usually improve spontaneously. In severe cases, however, blood transfusion and corticosteroids are indicated. Lusher and Zuelzer (1966) who analysed 152 cases of acute I.T.P. in children concluded that 92.6% of the untreated as well as 97.5% of the corticosteroid-treated gave uneventful recovery without recurrence of thrombocytopenia. On the other hand, in chronic I.T.P., where the immune mechanisms play a more important role than in acute I.T.P., administration of corticosteroids seems of little value. Harrington et al. (1951) found the presence of platelet antibodies in 8 out of 10 cases of chronic I.T.P. The importance of platelet antibodies which either destroy or inhibit platelet formation from megakaryocytes in the bone marrow, has been demonstrated by other investigators (Kuramoto, 1966; Rolovic et al., 1970).

Based on the presence of antiplatelet antibody, several authors tried to administer immunosuppressive agents to patients with chronic I.T.P. (Bouroncle and Doan, 1969; Lo et al., 1969). The purpose of this paper is to evaluate the effect of immunosuppressive treatment in children suffering from chronic I.T.P. refractory to prolonged treatment with corticosteroids.

Material and methods

Our material consisted of 6 cases (4 girls and 2 boys) admitted to the Dr. Tjipto Mangunkusumo General Hospital, Jakarta, with chronic I.T.P. Their ages varied from 4 to 8 years. All 6 cases were resistant to high

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dosage of steroid (4 mg prednisone/kg body weight daily) during 6 — 12 months of observation. Cases of chronic I.T.P. showing a leukemic picture on further examination were excluded from our material.

Immunosuppresive agents were given in combination with corticosteroids. Daily dose of immunosuppressive drugs, i.e. busulphan, 6-mercaptopurine, azathioprine, was as follows: 4 — 6 mg/kg body weight, 2.5 — 5.0 mg/kg body weight and 2 — 4 mg/kg body weight respectively. Next to getting corticosteroids, 3 cases (case no. 1, 4, 5) have been treated with busulphan, 6-mercaptopurine and azathioprine subsequently. Two cases (cases no. 2 and 3) received mercaptopurine followed by azathioprine, whereas case no 6 got entirely azathioprine. Routine peripheral blood examination was done once a week, but if required twice weekly. Bone marrow puncture was repeated in a regular interval of 2 — 3 months. Platelet antibodies were detected either by platelet agglutination (Dausset, 1966) or complement fixation (D'Amaro et al., 1970).

Results

Although low platelet count was observed in all cases, the number of megakaryocytes in the bone marrow was within normal limits. The maturation arrest at the stage of megakaryocytes was noted as a marrow picture lacking in metamegakaryocytes. All cases showed the presence of platelet agglutinins which was proven by the finding of 7 positive agglutination reaction among 10 donors.

From our study, it was observed that 6-mercaptopurine could only cause a temporary remission in one out of 5 children (case no. 2). After 1 month of treatment a normal platelet count was achieved, which could be maintained for 2 months. A decrease was thereafter observed in spite of continuing this drug for a period of four months.

None of the 3 patients treated with busulphan however, showed any sign of remission after 2 — 20 months of observation.

Azathioprine caused temporary increase of platelets in 2 out of 5 cases (cases no. 1 and no. 2). Remission of these 2 cases was recorded after 2 and 4 weeks of treatment, and lasted for a period of 10 and 4 weeks respectively. On further examination, the platelet count dropped towards below normal value, although the treatment was continued during the next 4 — 5 months.

Discussion

Many kinds of immunosuppressors and antimetabolites have been widely used in various non-malignant blood disorders. Since we have a limited supply of these drugs in our hospital, we will discuss only busulphan, 6-mercaptopurine and azathioprine.

Busulphan is less frequently used as immunosuppressor in this hematologic disorder. It has been tried out in thombocythemia and polycythemia by Storti et al. (1966) and Robertson (1970) without any result. Our experience is that this drug has also given unfavourable results, i.e. none of the cases treated with busulphan showed an increase in platelet count. Another immunosuppressive agent applied in our trial is purinethol which is used more frequently in our clinics, either as immunosuppressive agent or as cytostatic drug. Reiquam and Prosper (1966) have observed in their 3 cases of chronic I.T.P. that purinethol is neither useful in controlling clinical bleeding nor in elevating the platelet count. In our trial only one case out of five treated with purinethol revealed a transient normal platelet count.

The more effective and potent immunosuppressive agent is imuran, a heterocyclic derivative of mercaptopurine, in which a substituted imidazole ring replaces the hydrogen of the sulphydryl group. Various results have been stated in the literature. Lo et al. (1969) found no therapeutic effectiveness of azathioprine in the treatment of chronic I.T.P. On the contrary, Bouroncle and Doan (1969) reported a favourable result in which azathioprine was given in long term management of 17 patients with I.T.P., the majority being refractory to conventional therapy with splenectomy and corticosteroids. A complete hematologic remission was found in 12 patients whereas a temporary remission was detected in 2 cases. These authors are of the opinion that when the disease is refractory to splenectomy as well as to corticosteroids, or when prolonged application of corticosteroids is required, administration of azathioprine in combination with corticosteroids is recommended. Using azathioprine in our study, we do not find much therapeutic effectiveness in managing chronic I.T.P. Only in 2 cases out of 5, temporary remission has been observed, which is however followed by a drop of platelet count 1 month thereafter.

In summary, we come to a conclusion that busulphan is of no value in the treatment of chronic I.T.P., whereas purinethol and azathioprine can only cause a transient normal platelet count. This information, however, needs further evaluation due to the small number of our material.

The cause of failure in the treatment of chronic I.T.P. is not clearly understood. The low platelet count has been variously attributed to a decreased rate of platelet formation due to marrow inhibition, excessive platelet destruction by the reticulo-endothelial system and damage of megakaryocytes and platelets by a circulating antibody (Kura-

TABLE 1 : *Results of immunosuppressive drugs adminis.ration*

Case No.	Thrombo-agglutinin test	Busulphan			6-Mercaptopurine			Azat				
		Treatment until remission (month	of remission	treatment	Treatment mission (month)	ssion		mission (month)	ssion	Total treatment)	i-	o tment
1.	positive									no response	no response	
2.	posit								ive	—	—	—
3.	positive									—	—	—
4.	positive	no response	no response	2	no response	no response	7	no response	no response	6		
5.	positive				no response	no response	9	no response	no response	response	no response	
6.	posltive				—	—	—	no response		—	—	—

moto, 1966; Baldini, 1966; Rolovic et al., 1970). The findings of lipid containing splenic macrophages and foamy histiocytes (Salzstein, 1961; Benham and Taft, 1972) support the view that this phenomenon is a direct result of splenic phagocytosis. The role of immunologic mechanism appears to be a major cause in the pathogenesis of low platelet number in chronic I.T.P. (Harrington et al., 1951). The study of Pizzi et al. (1966) suggests a hypothesis that some plasma protein material is strongly adherent to the surface of megakaryocytes in more than 50% of cases of chronic I.T.P. As can be seen on the table below, in all our cases platelet antibodies have been detected. It is more likely that the failure of immunosuppressive drugs is primarily due to splenic defect, i.e. the spleen continues to phagocytize platelets and to produce platelet antibodies. Continued and excessive antibody production seems also to be the cause of drug resistance, where long term administration of purinethol and azathioprine resulted only in transient remission. That the spleen is suspected to be a source of platelet destruction has also been reported (Reiquam and Prosper, 1966). We suggest therefore that splenectomy should be performed in thrombocytopenic cases which fail to respond to corticosteroids and immunosuppressive agents. Some investigators (Brooks et al., 1969; Benham and Taft, 1972) have reported a favourable result of splenectomy with an overall remission rate between 50 — 82%.

Summary

The result of treatment with busulphan, purinethol, azathioprine in combination with corticosteroids in 6 children suffering from chronic I.T.P. has been reported. Busulphan is of no value, whereas purinethol as well as azathioprine caused transient remission for a couple of months in only 1 case and 2 cases respectively.

The possibility of continued and excessive platelet antibody production due to splenic defect has been suggested as the etiology of thrombocytopenia and the cause of drug resistance.

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