The Use of Vincristine in Refractory Auto-immune Thrombocytopenic Purpura

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SUMMARY

Two patients with auto-immune thrombocytopenic purpura are reported who continued to bleed despite high doses of corticosteroids, immunosuppressive therapy and splenectomy. The addition of vincristine to their therapeutic regimen produced a response in each case and both patients are now off all therapy without significant bleeding. It is suggested that this agent may be of value in selected cases where conventional regimens have failed or where splenectomy and corticosteroids are contra-indicated.

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The use of drug therapy in auto-immune thrombocytopenia is aimed at correction of the haemostatic defect by raising the platelet count, an effect achieved at a humoral level by interference with B-lymphocyte function so that antiplatelet auto-antibody is impaired either quantitatively or qualitatively. A further benefit of immunosuppressant therapy may be related to T-lymphocyte damage with impairment of cell-mediated cytolytic mechanisms directed against platelets; the latter are now thought to play a significant role in the pathogenesis of this disease.[1]

Corticosteroids are known to impair antibody production, to decrease thymic weight and to cause shrinkage in spleen size,[2] so that their use is likely to diminish platelet loss occurring on an immune basis. Splenectomy may further help by removing a reticulo-endothelial organ in which platelets are selectively sequestered while perhaps simultaneously abolishing the production of a splenic factor inhibiting thrombopoiesis.

The use of corticosteroids, with or without other immunosuppressive drugs, and splenectomy is an acknowledged form of management for auto-immune thrombocytopenia. However, when this therapeutic approach fails, other methods are urgently needed. In this regard the vinca alkaloids are of interest since their use was noted to result in thrombocytosis,[3] an effect subsequently confirmed experimentally in rats and mice,[4] and also reported during therapy with these agents in Hodgkin's disease and lymphocytic lymphoma. More specifically, thrombocytosis has been reported during the therapy of auto-immune thrombocytopenic purpura.[5,6]

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PATIENTS AND METHODS

We report 2 patients in whom splenectomy, followed by high dosage corticosteroids combined with immunosuppressives, was unsuccessful in controlling either the platelet count or the purpura, but in whom parenteral administration of vincristine raised the circulating platelet level, abolished the bleeding disorder and has made withdrawal of drug therapy possible.

Case 1

A 28-year-old White female developed widespread purpura and brisk epistaxis after ingestion of a proprietary preparation taken for upper respiratory tract infection.

Physical examination was negative, apart from extensive purpura. Her platelet count was 24 000/mm^3, haemoglobin 14 g/100 ml, and a total white cell count was 8 000/mm^3. Marrow showed increased numbers of megakaryocytes in which the morphological features of stimulated thrombopoiesis were evident. Antiplatelet antibodies could not be demonstrated. Serological evidence for lupus erythematosus was not demonstrated.

Prednisone was administered in a dose of 1 mg/kg/day with a good effect initially. Three weeks later the patient relapsed, probably because she had stopped taking her medication. She was readmitted and, in view of her unreliability in taking steroids, was submitted to splenectomy. There was an immediate increase in her platelet count to levels above 100 000/mm^3, and during the next three weeks her steroids were gradually reduced.

One month after this operation she again developed an upper respiratory tract infection, and took the same drug as before. She was readmitted profoundly thrombocytopenic, again with extensive purpura. Despite 120 mg prednisone daily, the patient deteriorated rapidly. Azathioprine was commenced at 2 mg/kg/daily, and she was given a single intravenous injection of 30 mg/kg of cyclophosphamide. Despite these measures, the platelet count remained below 10 000/mm^3 and she continued to bleed.

Thirty-six days after her relapse, and while receiving continuous corticosteroids and azathioprine with a platelet count of only 9 000/mm^3, she was given 2 mg vincristine intravenously. There was an immediate small elevation in her platelet count to 30 000/mm^3. Subsequently vincristine given at weekly intervals has had a progressively greater effect (Fig. 1).

To date the patient has received a total of 8 mg of vincristine and the platelet count now varies around

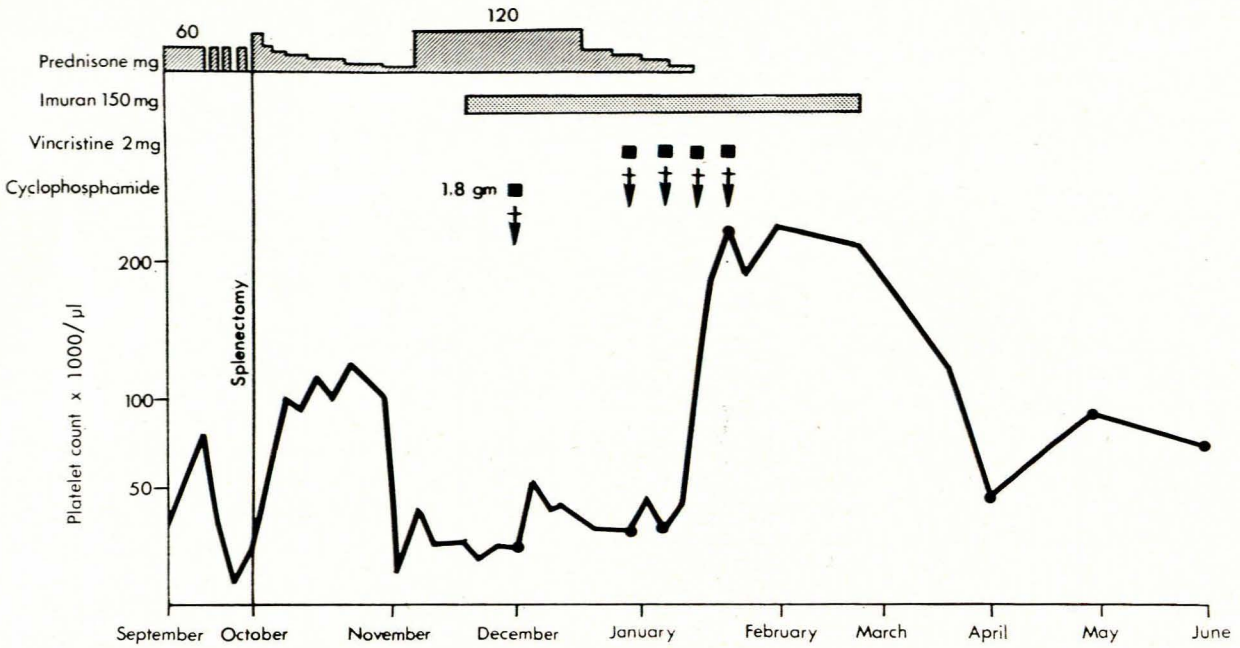

Fig. 1. Response in platelet count to splenectomy, and subsequently to immunosuppressive agents including vincristine. Note the progressively greater response to the initial doses of vincristine.

50 000/mm³. She has been off all other therapy for 9 months, and experienced no side-effects from the vincristine. No inappropriate bleeding is evident and menses are normal.

Case 2

A 14-year-old Black girl presented with widespread purpura, gingival bleeding and epistaxis. There was no history of preceding illness or drug ingestion.

Physical examination was normal, apart from extensive purpura. Platelet count was 12 000/mm³, total white cell count 8 000/mm³, and haemoglobin 5 g/100 ml. Reticulocyte count was 31%, probably related to extensive bleeding into the tissues,[7] with resorption of blood. Bone marrow showed an increase in the number and activity of megakaryocytes with associated erythroid hyperplasia and morphological evidence of combined iron and folate deficiency. Bilirubin and serum haptoglobin levels were normal. There was no urobilinogen in the urine, and the Coombs's test was persistently negative. Antiplatelet antibodies could not be demonstrated, and no evidence for the disseminated lupus erythematosus was found.

This 60-kg patient received 1 mg/kg prednisone daily for a week without effect. This was increased to 120 mg daily, and despite this, the platelet count remained low, the patient continued to bleed and required the transfusion of 18 units of blood.

In view of continued deterioration, emergency splenectomy was performed. After this operation there was still no improvement, and steroids were continued in high dose. Because this regimen was ineffective, azathioprine 2 mg/kg/day was commenced, and she received 1,2 g of cyclophosphamide intravenously. The platelet count over the next two weeks never rose above 10 000/mm³.

Twenty-five days after splenectomy and while still bleeding actively, with a platelet count of 1 000/mm³, she received 2 mg vincristine intravenously. This was followed by a rapid rise in her platelet count to 50 000/mm³. The count, however, dropped gradually over 7 days (Fig. 2). Subsequently she has received further injections at weekly intervals, and each was accompanied by a predictable rise in the platelet count, the effect initially becoming more pronounced with each successive dose. The platelet count reached about 200 000/mm³ while she was on vincristine, but since this drug was stopped, it has again dropped, although purpura and bleeding have not been a problem. All therapy, including vincristine, has been withdrawn, her platelet count remains between 50 and 100 000/mm³ and she is free from all abnormal bleeding. There are no side-effects from the vincristine, either clinically or when assessed on nerve conduction studies and electromyography.

DISCUSSION

Elucidation of the mechanism producing thrombocytosis after parenteral administration of vinca alkaloids in patients with auto-immune thrombocytopenia is complicated by the fact that there is no unanimity in the literature regarding the exact nature of the thrombokinetic lesion in this condition. It is generally agreed that platelets have a markedly shortened survival time in the circulation, and that this is associated with accelerated turnover of megakaryocytes in the marrow, often as much as 8 times the normal,[8] the megakaryocytes showing changes characteristic of stimulated thrombopoiesis.

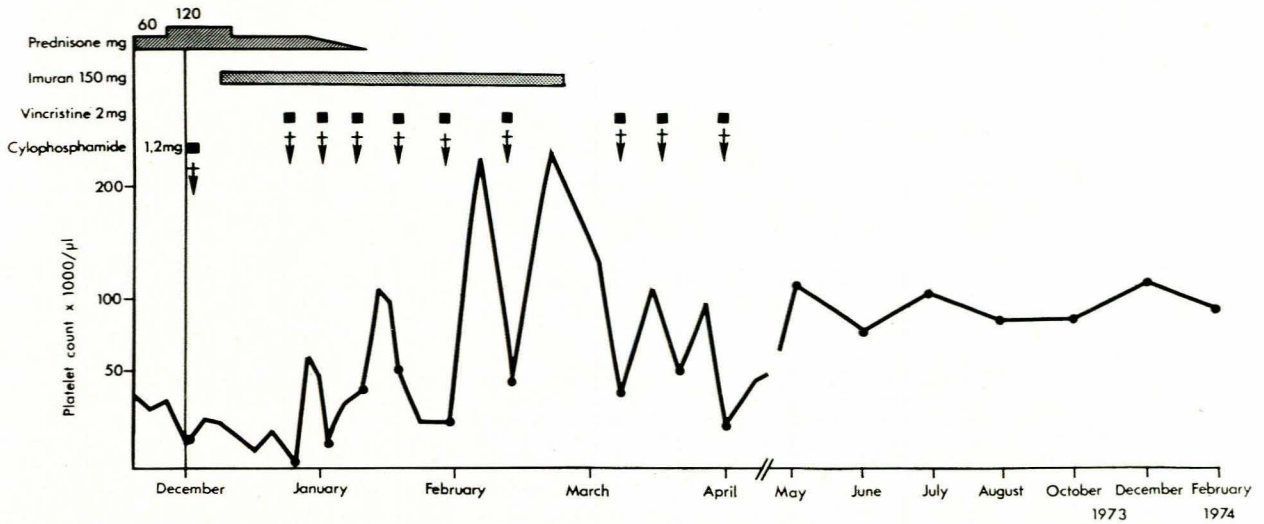

Fig. 2. Response in platelet count to postsplenectomy therapy with intermittent vincristine injection. Note the decreasing effect with latter injections of this alkaloid.

It has furthermore been suggested that this thrombocytopenia may reflect decreased platelet survival combined with either an actual decrease in marrow platelet production or an inability of the megakaryocytes to adequately compensate for the sharp decrease in platelet survival:[9] an effect possibly related to splenic inhibition of thrombopoiesis.

The vinca alkaloids are capable both of inhibiting platelet antibody biosynthesis[10] and increasing platelet production by the marrow.[4,11] If platelet output is already maximal then an effect on antibody biosynthesis would appear to be more significant. If, on the other hand, one accepts that platelet output is not necessarily maximal, these alkaloids may act by releasing an inhibition on the marrow.

It is noteworthy that a direct effect of the alkaloids on the platelets is loss of both the microtubules[12] and their discoid form, and it was speculated that such changes might impair aggregation and so lead to longer survival.[13] It is unlikely that this phenomenon could be implicated in the rising platelet count, particularly since no impairment of function was demonstrated.

The long-term effects of these agents require further investigation, particularly since there is one case reported[5] illustrating diminished augmentation of thrombocytosis with successive doses. It is interesting that this pattern was seen in our first patient, at least transiently, and was improved by reduction of the Imuran, suggesting that the response was modified by iatrogenic depression of thrombopoiesis.

Vincristine therapy in auto-immune thrombocytopenia would seem to offer benefit in selected patients refractory to splenectomy and corticosteroids,[14] and it is suggested that, although this agent is not the first choice of therapy in cases of auto-immune thrombocytopenia, its use might be seriously considered where conventional regimens have failed, or where splenectomy and corticosteroids are contra-indicated.

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