Clinical Use of Immunosuppressive Drugs: Part II

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Summary

In haematological diseases, insufficient data has been accumulated to evaluate the efficacy of immunosuppressive drug treatment in patients with erythroid aplasia or sideroblastic anaemia. Cyclophosphamide may be efficacious in inhibiting circulating anticoagulants in patients who need continued replacement of clotting factors.

Azathioprine, 6-mercaptopurine, cyclophosphamide and vincristine have been used successfully in treating patients with idiopathic thrombocytopenic purpura, and some patients with auto-immune haemolytic anaemia may benefit from the addition of purine analogues. However, the use of immunosuppressive therapy seems to accelerate the presence of haematological malignancies in patients with macroglobulinaemia.

In gastro-intestinal diseases, uncontrolled studies have shown nitrogen mustard, 6-mercaptopurine and azathioprine to be of modest benefit to patients with ulcerative colitis and Crohn's disease. In a controlled trial azathioprine plus prednisone proved more effective than prednisone alone in sustaining remission in patients with Crohn's disease. In patients with either chronic active hepatitis or primary biliary cirrhosis, however, there seems to be no benefit from immunosuppressive therapy for primary treatment of these diseases.

Cyclophosphamide, azathioprine and methotrexate have all been used with some success in treating patients with uveitis, and in a controlled trial cytarabine has been shown to be beneficial to patients with herpes ophthalmicus. However, no benefit has been shown to patients with the eye changes of Graves' disease with either azathioprine or methotrexate.

Patients with Paget's disease appear to be helped by mithramycin.

Cyclophosphamide, chlorambucil and azathioprine are ineffective in treating patients with multiple sclerosis. 6-mercaptopurine, azathioprine, methotrexate and cyclophosphamide have all produced some benefit in patients with myasthenia gravis, and some patients with idiopathic pulmonary haemosiderosis have responded to azathioprine, 6-mercaptopurine and cyclophosphamide.

Alkylating agents have proved useful in treating some patients with asthma and in treating frequent relapers among children with the nephrotic syndrome. In adults with membrano-proliferative glomerulonephritis some patients have responded to combination therapy with cyclophosphamide, azathioprine and corticosteroids. Immunosuppressive therapy is also indicated in prolonging graft survivals in patients receiving organ transplants.

Drug toxicities of immunosuppressive agents are discussed. Their long-term effects, including mutagenic potential, have as yet not been fully elucidated.

1 Second of a 2-part review. Part I appeared in previous issue.
2.3 Haematological Diseases

2.3.1 Erythroid Aplasia

There are many cases reported in the literature of erythroid aplasia and thymoma. Other disorders associated with thymoma seem to be related to abnormal immunological status, of which about 30% remit when the thymoma is removed. Several investigators have shown that the abnormality in erythroid aplasia is antibody directed against marrow erythroblasts. It is because of these two associations and the ineffectiveness of other treatment, that investigators have considered erythroid aplasia to be an auto-immune disease and that immunosuppressive drugs have been suggested in its treatment.

Five patients have been reported to respond to immunosuppressive therapy alone (Krantz, 1974; Krantz and Kao, 1967, 1969; Safdar et al., 1970). These remissions were induced by 6-mercapto-purine, azathioprine, cyclophosphamide, and cyclophosphamide plus prednisone. One patient (Krantz and Kao, 1969) responded to azathioprine after splenectomy, and while in remission the plasma no longer contained a gamma G inhibitor of haemoglobin. Three patients who were treated with prednisone, cyclophosphamide and horse anti-human thymocyte gamma G globulin, with remission for up to 3 to 12 years (Krantz, 1972), and three patients who after proving refractory to corticosteroids and androgens were treated with cyclophosphamide or cyclophosphamide plus anti-lymphocyte globulin (Marmont et al., 1975), have also been reported.

Clearly, more therapeutic study is needed before any judgement can be made about the use of immunosuppressive drugs in this uniformly fatal disease.

2.3.2 Sideroblastic Anaemia

Sideroblastic anaemia is a haematological disorder characterised by the presence of ring sideroblasts in bone marrow and defective haeme synthesis. There is an abnormal accumulation of iron in the developing erythroblast which is thought to be due to a mitochondrial defect. There is as yet no firm evidence of immunological disturbance.

A report of 1 patient has been published in which azathioprine therapy induced a prompt rise in haemoglobin (Zervas et al., 1974). Cessation of azathioprine led to exacerbation of the anaemia, but this again responded to a second course of therapy. However, no conclusions can be drawn from this one case.

2.3.3 Circulating Anticoagulants

Patients with haemophilia requiring replacement of factor VIII have a 6 to 21% incidence of developing antibodies inhibitory to that factor. Circulating anticoagulants can also occur spontaneously and in conjunction with connective tissue disorders.

Inhibition of circulating anticoagulants to clotting with cyclophosphamide has been reported (Bidwell, 1969; Dormandy et al., 1971; Green, 1968; Nilsson et al., 1973, 1974a,b). In one report 2 of 4 patients responded with successful haemostasis (Nilsson et al., 1974b). In another, azathioprine was found to be ineffective in suppressing levels of inhibition (Lechner et al., 1972).

Cyclophosphamide may be useful in inhibiting the development of antibody to clotting factors and may have some as yet undemonstrated role in treating patients who need repeated replacement of clotting factors. More data needs to be collected in a controlled fashion.

2.3.4 Idiopathic Thrombocytopenic Purpura (ITP)

Twenty-five years ago Harrington demonstrated that serum from a patient with idiopathic thrombocytopenic purpura contained a circulating anti-platelet factor. Since that time additional research has identified the factor as being gamma G immunoglobulin and that the spleen is one site where antiplatelet antibody is synthesised. The usual therapy for this disease is splenectomy which results in clinical cure in 70%, and corticosteroids