Ciclosporin (CyA) as Primary Treatment for Severe Acute Aplastic Anaemia*

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Summary

In adult patients with severe acute aplastic anaemia, primary therapy with CyA alone (n=6) was compared in a prospective randomised trial to an equivalent amount of this immunosuppressive agent in combination with antilymphocyte serum (n=6). At minimum follow-up of 36 months no response could be attributed to either regimen. Thus, the use of CyA, either on its own or in combination with antilymphocyte serum, cannot be recommended for this indication.

Introduction

Allogeneic bone marrow transplantation is the preferred treatment for patients under the age of 45 with severe acute aplastic anaemia having a suitable donor [3]. Without this option, supportive care [16] is essential, but anabolic androgens do not significantly alter the course of the disease [3]. The demonstration that antilymphocyte serum or antithymocyte globulin [6, 11] produced variable response rates suggested that in some individuals an immunologic mechanism may be active in pathogenesis. To further explore this possibility the immunosuppressive agent, CyA [14], was randomly given to consecutive patients with severe acute aplastic anaemia, either alone or in combination with antilymphocyte serum.

Materials and methods

Twelve patients with severe acute aplastic anaemia [2] were randomised to receive either CyA alone (n=6) or the same schedule of this agent with concurrent infusion of antilymphocyte serum (n=6). The trial was approved by the Ethics Committee of the University of Cape Town and Groote Schuur Hospital, and informed consent obtained from each patient. CyA was given at a loading dose of 25 mg/kg/day in two divided doses for one week, followed thereafter by a daily split schedule, with dosage adjustment using radioimmunoassay (Ciclosporin RIA Kit, Sandoz, Switzerland) [12] to maintain peak levels 4 hours after the dose between 300 and 500 ng/ml and trough levels between 200 and 400 ng/ml. Antilymphocyte serum (Merrieux, France) was administered by intravenous infusions over half an hour, at a dose of 15 mg/kg on each of 4 consecutive days. The CyA was continued for a minimum period of 3 months unless undesirable side effects necessitated withdrawal.

Patients who failed to respond after 3 months continued receiving CyA and, in addition, were given oral prednisone (0.5 mg/kg/day) in combination with oral oxymetholone (2 mg/kg/day), the latter being increased to the maximum tolerated dosage. All patients received standard supportive care in the form of red cell and platelet transfusion; appropriate antibiotics were given for infections.

Hematologic response was defined as a rise in platelet count above $50 \times 10^9$/l, absolute granulocytes above $1 \times 10^9$/l, and no red cell transfusion requirement [8].

Results

The median age of the patients was 27 years (range 12–49); there were 8 males
and 4 females. In none was there any ascertainable cause for the aplastic anaemia. The period from diagnosis to commencement of CyA varied from 1 month to 2 years. Three patients were lost to follow-up; one at 2 months and two at 18 months. One patient subsequently received bone marrow from an HLA identical and MLC non-reactive sibling, having initially elected to enter the trial of immunosuppressive therapy. Patients have been followed for a minimum of 36 months.

There was no sustained response in either group.

Two patients responded to therapy during the second phase of the study whilst receiving additional prednisone and oxy-metholone. In one patient the remission was sustained until he was lost to follow-up after 18 months. A second patient achieved a transient response only and died after 18 months of treatment, at which time she was again aplastic.

All patients are accounted for, having either died or been lost to follow-up; median survival was 8 months (3–36 months).

Some degree of toxicity occurred. With CyA administration, an elevation of serum creatinine and diminishing clearance was recorded in 6 of the 12 patients but was reversed following dosage adjustment in all but one, in whom the drug was discontinued. Tremor developed in 2, hirsutism in 1, hypertension in 1, and transient elevation of the serum bilirubin level in 3 patients. The antilymphocyte globulin resulted in serum sickness in one individual, and generalised convulsions occurred in a second patient.

Discussion

Severe acute aplastic anaemia may occur as a result of irreversible damage to the haematopoietic stem cell [1] although an indistinguishable syndrome can arise on an immunologic bases [15]. Most established cases do not respond to standard forms of immunosuppressive therapy, including adrenocorticosteroids and additional cyclophosphamide administration [7], but there have been reports of significant improvement following antilymphocyte serum and antithymocyte globulin [6, 11]. The decision to undertake this trial, evaluating CyA in previously untreated patients with severe acute aplastic anaemia, remains largely empirical. Available evidence for the action of this agent suggests that maximum efficiency would be anticipated at the time when antigen exposure first occurs [9] and this may account for the apparent lack of response in our patients.

The combination with antilymphocyte serum, anticipated to be additive to the functional lesions produced by CyA in abrogating a potentially cellular mechanism in the aplastic patients, was equally unsuccessful. The results of treatment with both antilymphocyte serum and antithymocyte globulin are variable and may reflect differences in dosage, duration of therapy, quality, and type of protein used [5, 15]. Because of the small number of patients in our series, it is not possible to draw any conclusions about the effect of either this particular product or the schedule used for its administration. However, the dosage was lower than had been reported in some trials, where a more favourable outcome was achieved [4]. Alternatively, the failure to obtain any response may be due to concurrent administration of CyA which modified the protein or its action, thereby rendering it ineffective. The subsequent administration of adrenocorticosteroids and anabolic androgens was included to ensure that any patients with hypoplasia rather than aplasia would not be compromised [13]. This approach would appear to be justified in view of the two patients where a response was documented.

CyA is acknowledged to have a range of toxic effects [10] and patients receiving this agent require scrupulous clinical and biochemical monitoring.

It is concluded from this data that CyA either as a single immunosuppressive agent or when used in combination with antilymphocyte serum has no place in treating patients with severe acute aplastic anaemia. The two responses in the present series are attributable to the subsequent administration of adrenocorticosteroids and anabolic androgens. It can, however, not be discounted that in one of these individuals the antilymphocyte serum may have had a minor or contributing role in the response.