mediate insulins are used to supply basal insulin requirements. A variation of 25% around a half time of 14 hours means that the same dose of insulin may produce hypoglycaemia on one day and good control or hyperglycaemia the next. Thus, the overnight period is the Achilles's heel of conventional insulin treatment,[15] and much of the minor adjustment of dosage is probably futile. The intermediate insulins are not precision tools.

Since the rate of absorption of NPH insulin depends on the dose the time scatter, and hence the unpredictability of clinical effect, will increase with the size of dose. This explains the success of treatment schedules based on multiple injections of soluble insulin during the day with small doses of NPH insulin last thing at night.[16] Soluble and intermediate insulin treatment given twice daily is not necessarily the treatment of choice for young insulin-dependent patients, and alternative regimens must be found if conventional treatment is to meet the challenge of portable infusion devices.

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Cyclosporin A as prophylaxis against graft-versus-host disease in 36 patients

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Abstract

Oral cyclosporin A was used as prophylaxis against graft-versus-host disease in (a) 31 patients with acute leukaemia or aplastic anaemia given transplants of HLA-matched bone marrow and (b) five patients with inborn errors of metabolism given transplants of haplotype-identical (parental) bone marrow. Twenty-six patients survived longer than two months after the operation. Despite the cyclosporin A, 31 patients (86%) suffered an acute form of graft-versus-host disease and 22 (61%) a chronic form. Nevertheless, the disease was usually treatable with immunosuppressive agents and caused the death of only one patient.

Cyclosporin A caused renal toxicity in all cases; occasionally this was associated with a "capillary leak" syndrome, fatal in two patients. In children hypertension, fits, and fluid retention were common side effects. Blood concentrations of cyclosporin A correlated with blood urea values and blood pressure but did not predict the occurrence of graft-versus-host disease. Four different dose schedules were used to find the optimum way to administer the drug.

Oral cyclosporin A is extremely effective at reducing the severity of graft-versus-host disease, but prevention of the disease is limited by toxicity of the drug and variable absorption. Better results might be achieved with parenteral administration or by using the drug in combination with other methods.

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Introduction

Graft-versus-host disease is a major complication of bone marrow transplantation. The disease is not completely understood but appears to be initiated by mature donor T lymphocytes.[1] The new immunosuppressive agent cyclosporin A, which

prevents clonal expansion of T lymphocytes after primary antigen challenge,[2] was found to reduce the morbidity and mortality associated with graft-versus-host disease when compared with methotrexate used as prophylaxis.[3 4 5]

In man the dose of cyclosporin A is limited by renal toxicity as well as by other, less severe side effects.[6-8] Few data are available on the absorption of oral preparations of the drug after bone marrow transplantation and the relation between blood concentrations of the drug and therapeutic effect or toxicity. One problem is the slow accumulation of cyclosporin A in the tissues after oral administration which may not reach effective values at the time the graft-versus-host reaction is initiated.

We have evaluated cyclosporin A in 36 consecutive patients with various conditions undergoing bone marrow transplantation. We measured blood concentrations of the drug to determine the pattern of absorption with different conditioning and preparative regimens, correlating blood concentrations with graft-versus-host disease and toxicity. Four dose schedules were investigated to determine the optimum method of oral administration.

TABLE I—*Preparation for bone marrow transplantation*

Disease	No of patients	Regimen before transplantation
Acute leukaemia	26	Cyclophosphamide 60 mg/kg day -3, -2; total body irradiation 9·5 g day 0 (23 patients) / Cytarabine 200 mg/m² + methylprednisolone 1 g/m² day -5, -4, -3, -2 Epipodophyllotoxin 200 mg/m² day -5; daunorubicin 40 mg/m² day -3, -2 Total body irradiation 9·5 g day 0 (three patients)
Aplastic anaemia	5	Cyclophosphamide 50 mg/kg day -5, -4, -3, -2
Inborn errors of metabolism	5	Busulphan 2 mg/kg day -11, -10, -9, -8 / Cyclophosphamide 2 g/m² day -5, -4, -3, -2

TABLE II—*Cyclosporin A schedules for prophylaxis against graft-versus-host disease*

Schedule	No of patients	Regimen
I	10	12·5 mg/kg from day -1 to day 100 after grafting with gradual dose reduction (except case 1)
II	6	1 g/m² from day -4 for seven days, 750 mg/m² for three days, 500 mg/m² to day 100 with gradual dose reduction
III	13 (4 mismatches)	500 mg/m² from day -4 to day 100 with gradual dose reduction
IV	7 (1 mismatch)	500 mg/m² from day -10 to day 50 with gradual dose reduction between day 50 and day 100 depending on presence or absence of graft-versus-host disease

Patients and methods

The procedure for bone marrow transplantation was as described.[9] All patients were managed in protective isolation during the period of neutropenia. Table I shows the preparation for transplantation for the different diseases treated. Thirty-one patients received bone marrow from HLA-identical, mixed-lymphocyte-culture-compatible donors. Five with inborn errors of metabolism received mismatched (haplotype-identical) marrow grafts from family members.

Except where otherwise stated, cyclosporin A (Sandoz) was given as an oral solution with or without a chocolate-masking agent (Caotina) in twice-daily doses according to the schedule (table II). In patients given mismatched grafts methotrexate (15 mg/m² on day 1 after transplantation and 10 mg/m² intravenously on days 3, 6, and 11) was given in addition to cyclosporin A as prophylaxis against graft-versus-host disease.

From May 1980 blood concentrations of cyclosporin A (measured 12 hours after the last dose) were monitored weekly by radioimmunoassay when assays became available.[10] Blood urea and electrolyte concentrations were monitored at least three times a week, together with regular blood pressure measurement, weighing, and liver function tests. Known features of toxicity such as abnormal hair growth, pigmentation, tremor, and anorexia were recorded.

Dose adjustment—When concentrations of cyclosporin A were

TABLE III—*Details of donors and graft recipients and outcome of transplantation*

Case No	Age and sex	Diagnosis*	Donor Sex	Donor Type†	Graft-versus-host disease Acute	Graft-versus-host disease Chronic	Days of survival (at 15/2/82)	Days off cyclosporin A (at/15/2/82)	Outcome at 15/2/82
1	32 F	AML	M	A	+		106	—	Death from relapsed leukaemia
2	17 F	ALL	M	A	+		626	441	Well
3	18 M	ALL	F	A			591	461	Well
4	7 F	ALL	F	A	+		528	386	Well
5	38 M	AA	M	A		+	482	330	Well
6	8 F	ALL	M	A	+		212	168	Death from relapsed leukaemia
7	2 F	AA	M	A	+		389	341	Well
8	9 F	ALL	M	A	+	+	374	281	Well
9	18 M	ALL	M	A	+	+	363	231	Death from relapsed leukaemia
10	26 M	ALL	F	A	+		63	—	Died of acute graft-versus-host disease
11	29 M	AML	M	A	+		66	—	Fatal capillary leak syndrome
12	11 F	AA	M	A	+	+	323	306	Capillary leak syndrome. Subsequently well
13	10 M	ALL	M	A	+	+	311	185	Recovering from acute viral myositis
14	18 M	ALL	F	B	+		46	8	Fatal capillary leak syndrome
15	4 M	ALL	F	A	+	+	298	189	Well
16	4 M	ALL	M	A	+	+	283	189	Interstitial pneumonitis requiring 50% oxygen
17	1 M	MPS (type I)	M	C	+	+	278	Continuing	Chronic skin graft-versus-host disease requiring cyclosporin A + prednisolone + azathioprine
18	26 M	ALL	F	A	+	+	276	116	Well
19	14 F	ALL	F	A	+	+	275	169	Well
20	14 M	ALL	F	A	+	+	248	118	Well
21	40 F	AML	M	B			234	154	Well
22	15 F	AA	F	A	+		233	90	Well
23	9 M	ALL	F	A			199	118	Well
24	15 M	ALL	F	A	+	+	177	12	Death from interstitial pneumonitis
25	2 F	MPS (type I)	M	C	+	+	174	Continuing	Chronic skin graft-versus-host disease requiring cyclosporin A + prednisolone + azathioprine
26	9 M	ALL	F	A	+		100	—	Death from relapsed leukaemia
27	10 F	ALL	M	A	+	+	157	Stepwise reduction	Well. No graft-versus-host diseases
28	7 M	ALL	F	A	+	+	150	Stepwise reduction	Capillary leak syndrome. Subsequently well
29	23 M	ALL	M	A	+	+	136	Stepwise reduction	Chronic graft-versus-host disease requiring cyclosporin A + prednisolone
30	16 M	AA	F	A			131	Stepwise reduction	Recurrent pancytopenia. Otherwise well
31	1 F	MPS (type III)	F	C	+	+	112	Continuing	Chronic graft-versus-host disease on cyclosporin A + prednisolone
32	1 F	MPS	F	C	+	+	112	Continuing	Chronic graft-versus-host disease on cyclosporin A + prednisolone
33	14 M	ALL	F	A	+		37	—	Death from disseminated aspergillosis
34	1 F	MLD	M	C	+		52	—	Death from cytomegalovirus infection
35	16 M	ALL	M	A	+	+	87	Stepwise reduction	Well. No graft-versus-host disease
36	14 M	ALL	M	A	+	+	72	Continuing	Chronic graft-versus-host disease requiring cyclosporin A + prednisolone

* AML = Acute myeloid leukaemia. ALL = Acute lymphoblastic leukaemia. AA = Aplastic anaemia. MPS = Mucopolysaccharidosis. MLD = Metachromatic leucodystrophy.
† Type A, HLA-identical, mixed-lymphocyte-culture-compatible family donor. Type B, HLA-identical, mixed-lymphocyte-culture-compatible unrelated donor. Type C, HLA-haplotype-identical, mixed-lymphocyte-culture-incompatible family donor.

below 100 μg/l in patients with graft-versus-host disease not responding to steroids the dose was increased by up to twofold until control was achieved. Two patients with concentrations below 100 μg/l were given the drug intravenously; failure of absorption was suspected due to severe diarrhoea and vomiting. When blood concentrations of cyclosporin A exceeded 1000 μg/l or hypertension, convulsions, severe fluid overload, or rapidly rising blood urea concentrations or values greater than 10 mmol/l (60 mg/100 ml) occurred, the next dose was omitted and the drug restarted at half to three-quarters of the dose. "Acceptable" side effects when the dose was not reduced included tremor, hirsuties, mild facial oedema, anorexia, and controllable hypertension.

Acute graft-versus-host disease—Skin graft-versus-host disease was diagnosed by a characteristic rash over the face, palms, and extensor surfaces, spreading to the trunk, and associated with compatible changes on skin biopsy.[11] Gastrointestinal graft-versus-host disease was diagnosed by diarrhoea (six or more stools/day) and vomiting, gut cramps, anorexia, and, in some cases, rectal or jejunal biopsy. Liver graft-versus-host disease was diagnosed when the alkaline phosphatase activity rose over 500 IU in the presence of raised alanine and aspartate transaminase activities. Acute graft-versus-host disease was treated (after other causes of fever and rashes had been excluded) with methylprednisolone 1 g/m² for three days, with dose reduction over 10-14 days in more severe cases. Repeat courses were given for relapse of symptoms.[9]

Chronic skin graft-versus-host disease was diagnosed by lichen-planus-like lesions in the mouth and tongue and lichen planopilaris lesions on the trunk and limbs associated with a lymphocytic infiltrate on skin biopsy.[12] Chronic reactions were treated with oral prednisolone 15 mg/m²/day with or without azathioprine 25 mg/m²/day. Treatment was withdrawn on disappearance of symptoms.

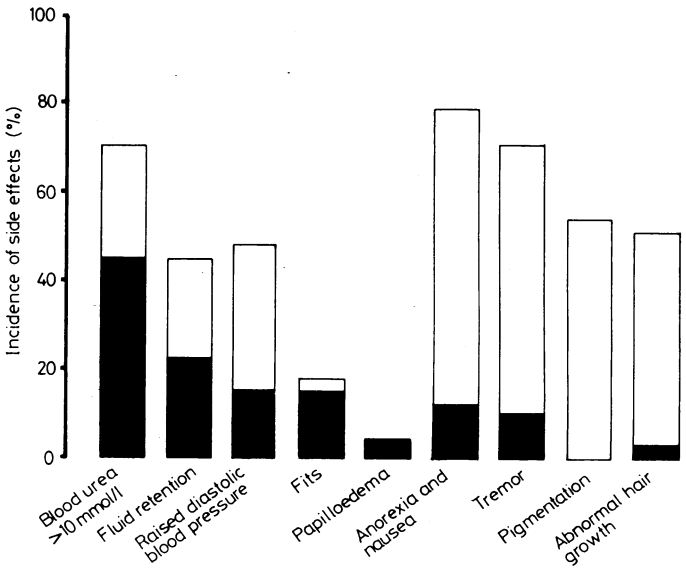

FIG 1—Percentage incidences of side effects of cyclosporin A. (Columns indicate total proportion of patients with each side effect. Black areas indicate proportion of patients with side effect necessitating reduction in dose of cyclosporin A.)

Conversion: SI to traditional units—Blood urea: 10 mmol/l ≈ 60 mg/100 ml.

Results

Outcome after transplantation—Twenty-six of the 36 patients were alive 72-626 days after transplantation (table III). The quality of life of the survivors was in general excellent, with 17 patients (excluding those with inborn errors) back at work or school. Sixteen of these patients had not needed cyclosporin A or any treatment for graft-versus-host disease for at least 90 days and showed no permanent disability from toxicity or graft-versus-host disease. Of the 26 patients given grafts for leukaemia, nine died—four from relapsed leukaemia, two with renal failure and respiratory complications, one with acute graft-versus-host disease, one from aspergillosis, and one from radiation-induced pneumonitis. One survivor remained oxygen dependent in hospital with residual lung damage from idiopathic pneumonitis. All five patients given grafts for severe aplastic anaemia were alive, four with normal haematopoiesis and one with recurrence of moderate pancytopenia in association with hepatitis-like changes in liver enzyme values. Four of the five patients with inborn errors given transplants with mismatched (parental) marrow were alive. One had died of cytomegalovirus infection 52 days after operation. Three of these patients had rejected the first transplant and required a second course of preparation before successful engraftment was achieved. The four survivors had left hospital but were continuing with cyclosporin A because of persisting chronic skin and liver graft-versus-host reactions.

Acute graft-versus-host disease occurred between days 9 and 84 in 31 patients (86%). In 16 it affected only the skin, in 12 the skin and gut, and in four the skin, gut, and liver. Three patients with skin, gut, and liver graft-versus-host disease were retransplanted with grafts from mismatched donors, and the fourth (case 10; table III) was the only patient whose death was directly attributable to graft-versus-host disease. With this exception, the acute disease was controlled by up to three courses of methylprednisolone. In 14 of these patients the dose of cyclosporin A was also temporarily increased.

Chronic graft-versus-host disease during treatment with cyclosporin A occurred between days 30 and 104 in 20 patients (56%). Nineteen had already had one or more episodes of the acute reaction. The disease was of mild or moderate severity, the major problem being failure to gain weight owing to anorexia or sore mouth. In two patients chronic forms of the disease had begun de novo on days 62 and 250 after cyclosporin A had been stopped. All patients had responded to low doses of prednisolone with or without azathioprine, but six (including patients with mismatched grafts) still needed treatment with prednisolone, azathioprine, and cyclosporin A.

Side effects of cyclosporin A—Figure 1 shows the side effects of cyclosporin A and their severity (as indicated by need to reduce the dose). Blood urea increased in all patients in the first 15 days of treatment. In 25 patients concentrations rose above 10 mmol/l (60 mg/100 ml), and in five of these the values were over 20 mmol/l, three developing oliguric renal failure. In four patients renal failure was associated with a capillary leak syndrome; these patients developed massive fluid retention, high blood urea concentrations, a vasculitic rash, and gastrointestinal blood loss with or without hypoxia, which in two required pulmonary ventilation. Skin graft-versus-host disease was absent or minimal in these patients both clinically and on biopsy. Despite stopping cyclosporin A two patients died from renal and respiratory failure. Also many patients developed some degree of abnormal hair growth, anorexia and nausea, weight loss, tremor, and pigmentation. In five patients these necessitated reducing the dose (fig 1). Abnormalities of liver function were uncommon and usually attributable to viral illness of graft-versus-host disease. No long-term damage from cyclosporin A was detected in the surviving patients who had stopped the drug. There was no difference in toxicity between different disease groups or the regimens of preparation for trans-

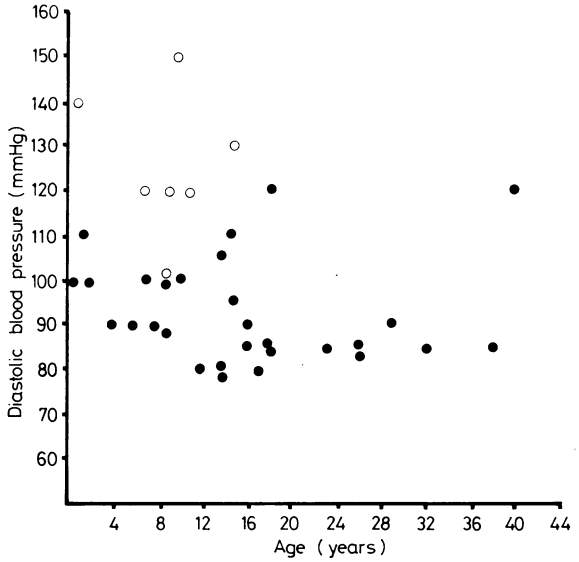

FIG 2—Highest diastolic blood pressures recorded during hospital stay after transplantation in patients of all ages taking cyclosporin A. ○=Patients with fits and hypertension. ●=Patients without fits.

plantation, but susceptibility to hypertension and fits was clearly age related, with children under 15 being particularly at risk (fig 2).

Relation of blood concentrations of cyclosporin A to graft-versus-host disease and toxicity—Trough blood concentrations of cyclosporin A did not correlate clearly with either the incidence of graft-versus-host disease or toxicity. Occasionally patients with undetectable concentrations of the drug had serious toxicity, while some patients with high concentrations developed graft-versus-host disease (fig 3). Patients with severe aplastic anaemia differed from the others in achieving large and rapid rises in blood cyclosporin A concentrations after transplantation, but only one patient developed serious toxicity necessitating stopping the drug. Circulating concentrations of the drug correlated closely with blood urea values ($r=0{\cdot}35$; $p<0{\cdot}001$), and diastolic blood pressure correlated nearly as well with blood urea values ($r=0{\cdot}22$; $p<0{\cdot}005$) as with blood cyclosporin A concentrations ($r=0{\cdot}24$; $p<0{\cdot}001$) (Spearman's rank correlation).

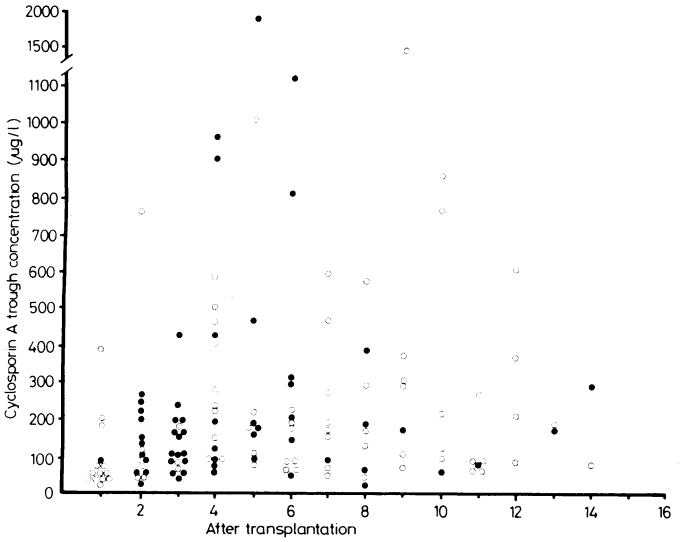

FIG 3—Trough concentrations of cyclosporin A each week after transplantation (36 patients). ○=No active graft-versus-host disease. ●=Graft-versus-host disease requiring treatment in that week.

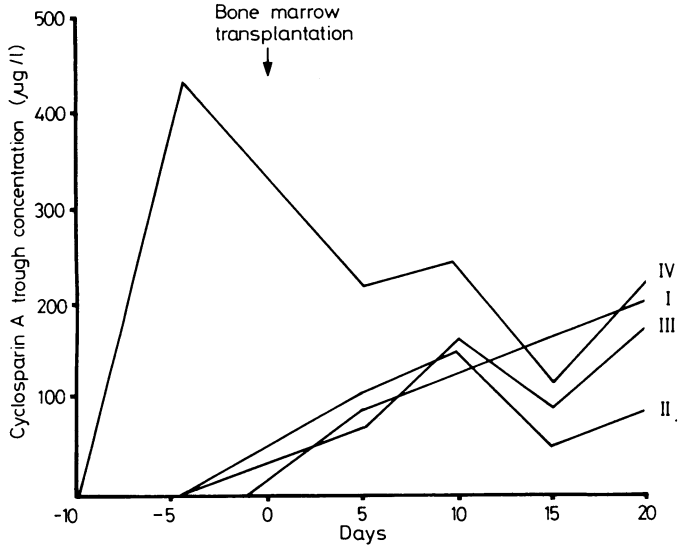

FIG 4—Changes in serum trough concentrations of cyclosporin A with different treatment schedules. (Schedule I 10 patients; schedule II 6 patients; schedule III 13 patients; schedule IV 7 patients.)

Effect of different dose schedules—Figure 4 shows the patterns of blood cyclosporin A concentrations achieved with the four dose schedules (listed in table II). The rate of accumulation of the drug was not increased by doubling the dose (schedule II), but when administration was started 10 days before transplantation (schedule IV) high blood concentrations were achieved in the first 15 days after transplantation. At day 10 after operation patients given schedule IV had mean concentrations of 245 µg/l compared with a mean of 150 µg/l in patients given schedules I, II and III. Figure 5 shows the results with the four schedules (patients with mismatched grafts are excluded since they were not evenly distributed through the different schedules). There was no significant difference in the incidence or severity of acute or chronic graft-versus-host disease in any schedule. Toxicity was a major feature of schedule II: four of the six patients developed renal failure, and two died from a combination of renal failure and lung complications. Because of these complications only six patients were treated with this schedule.

Discussion

Treatment with cyclosporin A was associated with a significant decrease in severity of graft-versus-host disease and overall mortality from bone marrow transplantation, but the incidence of the complication remained unchanged.[3-5] In these patients we decided to treat acute graft-versus-host disease primarily with methylprednisolone rather than increase the dose of cyclosporin A (except when failure of drug absorption was suspected). This was because of the risk of renal toxicity with high doses of cyclosporin A and the evident failure of high blood concentrations of the drug to modify acute graft-versus-host disease in some patients. With this combined immunosuppressive approach we controlled the complication satisfactorily without major toxicity from cyclosporin A or steroids. Cyclosporin A was equally ineffective at preventing chronic graft-versus-host disease, but this complication was mild and readily controllable with low doses of prednisolone and azathioprine.

Despite careful dose adjustment toxicity from cyclosporin A was an important problem. The major complication was renal impairment usually associated with fluid retention. Particularly at risk were children under 15, who also tended to have convulsions when hypertensive. An associated side effect was the "capillary leak" syndrome seen in four patients. The pneumonitis, skin and mucosal bleeding, and renal damage could all be accounted for by generalised endothelial and epithelial cell toxicity of the drug. While the complication has been described in association with mismatched transplants, we have seen the problem only in patients receiving cyclosporin A, suggesting that the drug may potentiate pre-existing endothelial cell damage provoked by other processes.

Other side effects from cyclosporin A such as tremor and hair growth were not serious and were reversed when the drug was withdrawn.

While blood concentrations of cyclosporin A showed good general correlation with blood urea values and hypertension, they did not accurately predict renal failure or capillary leakage in individual patients. Our results show that measuring blood urea concentrations and diastolic blood pressure is at least as useful as monitoring drug concentrations in preventing toxicity from cyclosporin A. Equally important in determining toxicity was the dose used. When the daily dose was doubled serious toxicity occurred, which prevented further application of this schedule.

Because of the inability to prevent graft-versus-host disease and the problem of toxicity, we tried several oral dose schedules to find an optimum way to administer cyclosporin A. These studies showed that it was possible to achieve measurable blood concentrations at the time of transplantation if the drug was started on day 10 before operation (schedule IV). Double doses of cyclosporin A from day −4 (schedule II) did not produce a significantly different pattern of blood cyclosporin A concentrations than schedules where the drug was started at a standard dose on day −1 or −4. Despite the ability to achieve early measurable blood concentrations of the drug with schedule IV, we were disappointed that the incidence of acute graft-versus-host disease in the first 14 days after operation was not affected. These results do not therefore support the hypothesis that

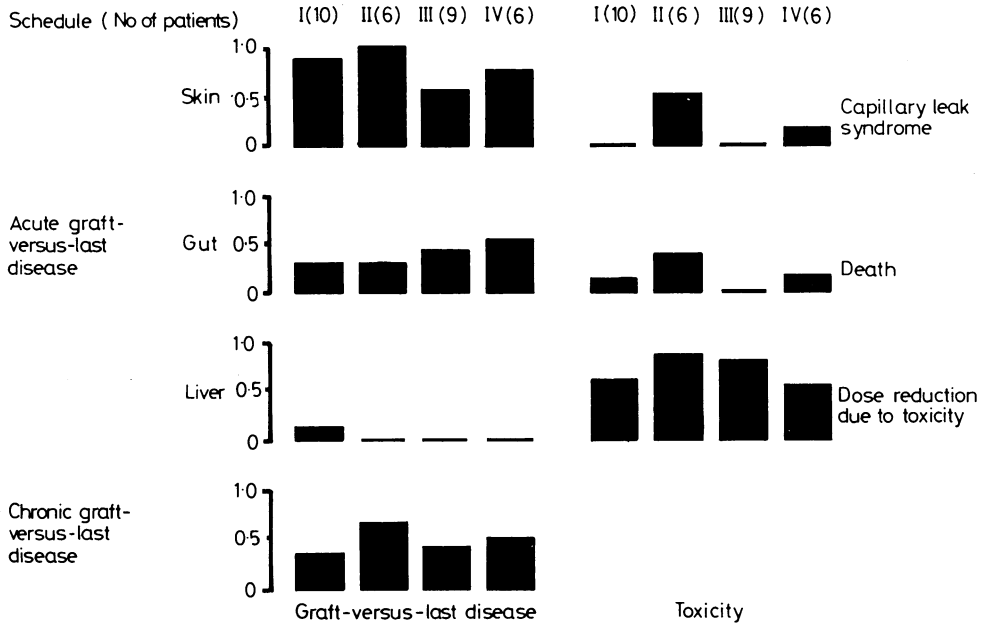

FIG 5—Influence of different cyclosporin A treatment schedules on graft-versus-host disease and toxicity in 31 matched patients with transplants.

cyclosporin A is more effective at preventing graft-versus-host disease if it is present in measurable amounts in the blood on the day of transplantation. Arguably, however, higher doses are necessary to prevent the complication, but toxicity is a limiting factor. Common to all schedules were low blood concentrations of the drug around 15 days after operation, suggesting that the chemotherapy and radiotherapy before transplantation temporarily affected gastrointestinal absorption of the drug. This erratic absorption may be a major obstacle to using oral cyclosporin A to prevent graft-versus-host disease.

The duration of treatment with cyclosporin A needed to protect against graft-versus-host disease is controversial. Other groups have given the drug for up to one year after transplantation.[4 5] We decided to stop cyclosporin A after 100 days, since we find that acute graft-versus-host disease does not occur after this time in patients given methotrexate. In our first patient given cyclosporin A an acute graft-versus-host reaction occurred when the drug was stopped abruptly, hence where possible the dose was tailed off over 30-40 days in subsequent patients. This resulted in only two patients developing the chronic reaction after stopping cyclosporin A. In several patients, however, the drug was stopped abruptly or reduced before 100 days because of toxicity; and in patients with mismatched grafts persisting chronic graft-versus-host disease necessitated continued treatment past 100 days.

In conclusion our results show that cyclosporin A plays a major part in preventing the serious consequences of graft-versus-host disease. While toxicity may be largely avoided by careful monitoring of drug concentrations, blood urea values, and blood pressure, manipulating the oral dose within the limits of toxicity is unlikely to be associated with improved prophylaxis against the complication.

Further improvements in preventing graft-versus-host disease may be achieved only by using parenteral cyclosporin A or by combining this drug with other techniques for preventing the complication, such as eliminating mature T lymphocytes from the harvested marrow.[13–15]

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