British Journal of Dermatology (1988) **119**, 73–77.

Intermittent high-dose dexamethasone-cyclophosphamide therapy for pemphigus

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Accepted for publication 23 February 1988

SUMMARY

Since 1982, we have treated 79 pemphigus patients with an arbitrarily designed regimen of 100 mg dexamethasone dissolved in 5% glucose given by an intravenous infusion over 1 h, daily on 3 consecutive days and in addition, 500 mg cyclophosphamide on day 1 only. The intermittent high doses (IHD) of dexamethasone are repeated every 2–4 weeks, and the patient continues to take 50 mg/day oral cyclophosphamide.

This treatment is divided into four phases. During Phase I, the patient continues to develop relapses of pemphigus a variable number of days after IHD, but the lesions heal up quickly after IHD. These relapses become progressively milder and stop after a few months, but the IHD are continued once a month for 6–9 months (Phase II). In the next phase (Phase III), the monthly IHD are stopped, and the patient continues to take 50 mg/day cyclophosphamide orally. After approximately 1 year this maintenance treatment is withdrawn and the patient is observed for any relapses (Phase IV).

Of the 79 patients treated, 10 patients have been lost to follow-up and two have died, one due to leukopaenia caused by inadvertent additional administration of methotrexate, and the other of an unknown cause. Of the remaining 67 patients, 25 are off treatment (Phase IV), 25 are taking only 50 mg cyclophosphamide daily (Phase III), ten are also in remission, but still receiving intermittent high doses of dexamethasone-cyclophosphamide (Phase II), and seven still have active disease (Phase I). The remissions are long lasting, being already more than 2 years in 17 patients (maximum 46 months), 1–2 years in 11 and less than 1 year in 32.

Side-effects of corticosteroids and cyclophosphamide are minimal and not clinically significant except for increased susceptibility to infections.

A variety of drugs and therapeutic regimens have been used for the treatment of pemphigus, but pemphigus continues to be a potentially fatal disease,[1] death being due either to the disease or to the complications of treatment.[2–6] Our personal past experience with pemphigus has been similar.[7] Early intensive treatment can, however, significantly reduce the mortality and morbidity of this disease.[8]

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In 1982, we started using an arbitrarily designed combination of high dose dexamethasone and cyclophosphamide intermittently, and low dose cyclophosphamide continuously. Subsequently, we reported[9] the two chief advantages of this regimen, which are rapid healing of the pemphigus lesions, so that in-patient therapy was reduced to only 4–5 days at a time, and freedom from such side-effects as obesity, osteoporosis, hypertension, diabetes, and peptic ulceration caused by prolonged corticosteroid therapy.

Two years ago, we observed that a proportion of our patients treated earlier with this regimen, were in remission even after they stopped receiving treatment, and the disease-free remissions in some cases were 2 years or longer.[10] We have subsequently treated more patients with this regimen, the results of which we now report.

METHODS

The diagnosis of pemphigus was made on clinical criteria, Tzanck smears and histopathology. Immunofluorescence studies were not undertaken due to lack of facilities. Laboratory evaluation included haemoglobin, total and differential leukocyte counts, platelet counts, ESR, blood glucose, blood urea, SGOT, SGPT, serum alkaline phosphatase, serum electrolytes, urinalysis, stool examination for occult blood and chest X-ray. All were undertaken before starting treatment and during follow-up. In addition, periodic examination for cataracts, stria atrophicans, blood pressure, history of epigastric pain, weight change, hair loss and urinary symptoms were carried out to record side-effects of corticosteroids and cyclophosphamide.

The treatment regimen used consisted of two components. These were intermittent high dose (IHD) therapy consisting of 100 mg dexamethasone in 5% glucose given by a slow intravenous infusion over a period of 1–2 h on 3 consecutive days, together with 500 mg cyclophosphamide given in the same intravenous drip on the 1st day only, and continuous low dose (CLD) therapy consisting of one tablet of 50 mg cyclophosphamide daily orally between the courses of intermittent high dose therapy.

The entire treatment was divided into four phases. During the first phase, pemphigus lesions would heal rapidly following the IHD, but after a variable number of days, new lesions would appear. IHD was repeated every 2–4 weeks depending upon the state of clinical activity, while CLD was continued irrespective of the results. After a variable number of courses of IHD, the relapses would start becoming milder and ultimately the patient would go into the next phase, the phase of remission while on therapy. During this phase (Phase II), the courses of IHD were repeated every month for a period of at least 6 months, and CLD continued. After the patient had remained in remission for a minimum of 6 months, the courses of IHD were stopped, but CLD was continued (Phase III). After 1 further year of Phase III, CLD was withdrawn, and the patient was followed up without any treatment (Phase IV).

RESULTS

Between January 1982 and May 1987, 79 patients (74 pemphigus vulgaris, three pemphigus foliaceus, and two pemphigus erythematosus) aged between 10 and 60 years, were treated with this regimen. Of these, 10 patients have been lost to follow-up and two have died. Of the remaining 67 patients, 60 patients are in remission at the time of writing, while seven are relapsing between IHD courses. In 25 patients all treatment has been withdrawn (Phase IV), and 25 patients are receiving only a maintenance dose of cyclophosphamide (Phase III). In 10 patients, the remission is recent and these patients are still in Phase II (Table 1). At the time of

TABLE 1. Current status of pemphigus patients treated with dexamethasone-cyclophosphamide (DC) regimen

Year of starting treatment	Total no. of patients treated	No. of patients with disease					
			In remission				
		Active Phase I	With DC Phase II	Cyclophosphamide only Phase III	No treatment Phase IV	Lost to follow-up	Died
1982	4	—	—	—	3	1	—
1983	8	1	2	1	3	1	—
1984	7	—	1	1	3	1	1
1985	19	1	1	6	9	2	—
1986	31	3	5	12	6	5	—
1987	10	2	1	5	1	—	1
Total	79	7	10	25	25	10	2

writing nine of the patients treated in 1982, 1983 and 1984 are already on no treatment and free of any clinical evidence of disease, while the patients who still have active disease are either those who started the treatment recently, or those who are irregular in presenting for IHD.

The duration of continuous remission in these patients is more than 2 years (maximum 46 months) in 17 patients, between 1 and 2 years in another 11 and less than 1 year in 32.

Of the two deaths, one patient died of septicaemia due to leukopaenia following inadvertent administration of methotrexate in addition to the regular regimen, while in the other the cause of death could not be ascertained.

Side-effects

The most important side-effect was secondary pyogenic infections of the skin lesions and candidosis of the mouth, while the disease was active. Most of the patients needed frequent courses of systemic antibiotics and oral nystatin. Once the skin and mucosal lesions had healed, increased susceptibility to infections was not seen. In three cases, pulmonary tuberculosis was reactivated, but appropriate antitubercular treatment given concomittently was able to control the infection.

There was no significant change in the laboratory parameters; leukocyte counts, blood glucose and electrolyte levels, and liver function tests remained within normal limits.

In one diabetic patient, the blood glucose levels were 300 mg/dl before the intermittent high dose, 360 mg/dl immediately after the IHD, 320 mg/dl after 1 h and 280 mg/dl after 2 h.

In another patient, total and differential leukocyte counts estimated on alternate days for 1 week during Phase I remained within normal limits. Leukopaenia observed in the patient who died was due to the additive effect of methotrexate. None of the other patients developed leukopaenia or thrombocytopenia. The significance of diffuse hair loss is difficult to evaluate, because, in several patients, the hair regrew during continued therapy. No patient complained of cystitis. Effects on gonads have not yet been evaluated.

None of the patients gained weight over and above any already gained due to previous corticosteroid therapy. Those patients who had already developed corticosteroid obesity, returned to a normal appearance.

Hypertension, peptic ulceration, cataracts, osteoporosis and striae were not seen unless already present before starting the present treatment.

Four patients developed a general darkening of the complexion, another four complained of generalized pruritus of the skin and nine experienced generalized discomfort after the intermittent high-dose.

DISCUSSION

It is generally believed that the prospects for complete cure of pemphigus are poor. In 1984, Lever and Schaumberg-Lever,[8] suggested that intensive therapy in the early stages of the disease may help to induce complete remission, and pemphigus could be regarded as a self-limiting disease. Our findings suggest that with the regimen reported here, it is possible to induce long-term remissions. Only those patients who did not receive the treatment regularly, continued to have relapses of the disease. With continued treatment, progressively more and more patients could be brought into remission. The duration of the phase of clinical activity after starting this regimen (Phase I) was very variable and it did not seem to depend upon factors such as the initial severity of the disease. Mucosal lesions responded last, and some of the patients with continuing disease activity have recurrences of mucosal lesions only. Once, however, the patient went into the remission phase (Phase II), the disease generally remained in remission.

Systemic corticosteroids and cyclophosphamide, given separately or in combination, are both well established methods of treatment for pemphigus. Intermittent high doses or pulse therapy of corticosteroids, generally methyl prednisolone, have also been used to control acute exacerbations of several immunologically based diseases. Our innovation lay in using the combination of intermittent high dose corticosteroids and cyclophosphamide in this particular dosage schedule. Our preference for dexamethasone over methyl prednisolone was based only on availability, and we believe that any other corticosteroid in equivalent doses may be able to achieve similar results. Similarly, methotrexate, azathioprine or other immuno-suppressive drugs may be as effective or even better. So far, we have not observed any serious side-effects with this regimen, but more experience is required. Minor and reversible side-effects are not worrying, but the effect of this regimen on the gonads needs to be evaluated because a proportion of pemphigus patients are children and young adults.

There is a general impression that in India pemphigus is a milder disease than the pemphigus that occurs in America or the Eastern European countries and this may in part account for our good results. However, recovery of even the most severely affected of our patients strengthens our faith in this regimen.

Our choice of drugs, their dosages and the duration of different phases of treatment, especially Phases II and III, were arbitrary. There is ample scope for further experimentation and modifications to work out the most appropriate regimen. The most important observation is that once the patient went into remission, there were no recurrences even after maintenance treatment was withdrawn, suggesting that possibly, the disease in these patients has been extinguished. However, immunofluorescence studies for autoantibodies and long follow-up will be essential to confirm a cure. The exact duration of follow-up before a patient can be considered to have recovered from pemphigus is not established, but the natural history of the disease suggests that a minimum of 2 years treatment-free disease-free follow-up should elapse before claiming a cure, although the longer the follow-up, the more certain one can be on this point. In addition, negative immunofluorescence tests on at least two occasions, 1 year apart, during this follow-up, can be taken as another criterion of a 'cure'.

The purpose of the present report is to encourage other centres to initiate a wide evaluation of our regimen, and to initiate trials of further modifications of this regimen to establish optimal dosage schedules.

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