ORIGINAL CONTRIBUTIONS

FURTHER STUDIES ON PEMPHIGUS PATIENTS TREATED WITH DEXAMETHASONE-CYCLOPHOSPHAMIDE PULSE THERAPY

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Our regime for the treatment of pemphigus consists of 100 mg dexamethasone dissolved in 5% glucose given by a slow intravenous drip over 1-2 hours and repeated on 3 consecutive days. On the first day, 500 mg cyclophosphamide is also given in the same drip. Such dexamethasone cyclophosphamide pulses (DCP) are repeated once a month. In between the DCP, the patient is given only 50 mg cyclophosphamide daily orally. During the first few months of starting this treatment, most patients continue to get relapses of pemphigus lesions in between the DCP (phase I). After a variable period however, almost all patients stop having such relapses, but we continue to give once-monthly DCP for at least 6 months (phase II), after which the DCP is stopped and the patient continues to take 50 mg cyclophosphamide daily orally for a further period of one year (phase III). At the end of this phase all treatment is stopped and the patient is followed-up for any relapse (phase IV). Follow-up of the first 100 patients, pemphigus vulgaris (92), pemphigus foliaceus (6) and pemphigus erythematosus (2), has revealed that 76 patients are already in remission (26 in phase IV, 35 in phase III and 15 in phase II), 7 patients are still having active disease (2 having been recently taken up for DCP, 3 being not regular, and 2 having only residual oral ulcers), 4 patients have died (only one of them because of an uncontrolled disease), while 13 have been lost to follow-up. The duration of remission has already been more than 2 years (maximum $4\frac{1}{2}$ years) in 22 patients. The only side effects with this regime consisted of increased susceptibility to pyogenic and candidial infections of the skin and oral mucosa during phase I and II and reactivation of tuberculosis in 4 cases which were managed with appropriate concomittent therapy. Other commonly encountered side effects of prolonged corticosteroid and cyclophosphamide therapy were not observed. We feel that this regime may prove curative for pemphigus and thus deserves to be tried on a large scale.

Key words : Pemphigus, Treatment, Curative, Dexamethasone, Cyclophosphamide.

Since 1982, we have been treating our pemphigus patients using a regime consisting of a very high dose of dexamethasone combined with cyclophosphamide given once a month (DC pulse), along with a low non-toxic dose of cyclophosphamide given every day in between the DC pulses.[1] This was an arbitrarily designed regime, meant to reduce the side effects of prolonged corticosteroid therapy and this was adequately achieved.[1] Subsequently however, it was noticed that 5 of the 6 patients treated during 1982 and 1983, and available for follow-up, were not having active disease and they had already stopped taking any treatment.[2] This disease-free and treatment-free period was quite remarkable compared to the course of the disease in these very patients before the institution of our treatment regime. Subsequently therefore, we have treated many more pemphigus patients with this regime, and the results seem to be similar.[3] It seems possible to induce almost every pemphigus patient into

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a remission which does not show any tendency for reactivation even after the treatment has been withdrawn completely. Although a much longer follow-up is necessary to see if pemphigus will get reactivated in any of these patients, the current status of these patients is encouraging enough to lead to the question, "Is it possible that these remissions are permanent and we have hit upon a regime which will be curative for this potentially fatal disease?" Data on the first 100 cases treated between 1982 and 1987 is being presented. This includes the data presented in the earlier reports.[1-3]

Materials and Methods

The diagnosis of pemphigus in each case was based on clinical characteristics, Tzanck smears from the base of blisters and histopathology of skin/mucous membrane lesions. Direct immunofluorescent staining was generally not done; but indirect immuno-fluorescent tests on the sera of some patients done subsequently showed titres varying between 1 : 10 to 1: 320. These patients were also evaluated for their basic parameters such as haemoglobin, TLC, DLC, platelet counts, blood sugar and urea, serum electrolytes, serum bilirubin, glutamic and pyruvic transferases, occult blood in stools, X-ray chest and bones, ophthalmic examination and other signs/symptoms of corticosteroid and cyclophosphamide toxicity. These evaluations were undertaken periodically during the course of treatment and follow-up.

The treatment regime consisted of 100 mg dexamethasone dissolved in 5% glucose given by a slow intravenous drip over 1-2 hours and repeated on 3 consecutive days. On the first day, 500 mg cyclophosphamide was also combined with dexamethasone in the same drip. Such dexamethasone cyclophosphamide pulses (DCP) were repeated once a month. In between the DCP, the patient was given only 50 mg cyclophosphamide orally daily, but corticosteroids were generally not given.

The course of the disease and follow-up have been divided into four phases. During phase I, the lesions would heal very quickly following DCP, but after a variable number of days, there would be a recurrence of the lesions. With repeated DCP however, the recurrences would become milder and milder till the patient went into complete remission. During the next phase, the patient would remain in complete remission but we continued to give one-monthly DCP and daily cyclophosphamide (50 mg orally) for a minimum of 6 months (phase II). After this, the DCP were stopped but the patient continued to receive a maintenance dose of 50 mg cyclophosphamide a day orally for the next 1 year (phase III). If still the patient continued to be in remission, even this treatment was stopped, and the patient was then followed-up without any treatment for any recurrences (phase IV).

The clinical course of the disease and the treatment in every patient were charted on a graph (Fig. 1) for easy reference. The patients were allowed to take regular baths with soap and water even during the phase of clinical activity. They were encouraged to apply topical corticosteroid-antibiotic ointments on ulcerated lesions; and also given systemic antibiotics and other drugs needed for their concomitant diseases if any. Sodium restriction, and administration of potassium, anabolic hormones, calcium and other adjuvants were as a rule not necessary.

Results

The 100 patients included pemphigus vulgaris (92 cases), pemphigus foliaceus (6) and pemphigus erythematosus (2). There were 55 males and 45 females. Their ages ranged between 10 and 65 years when they were enrolled for treatment. The duration of the disease before treatment was more than 10 years in 1, 5-10 years in 8, 2-5 years in 24 and less than 2 years in 67 cases. Twelve patients were

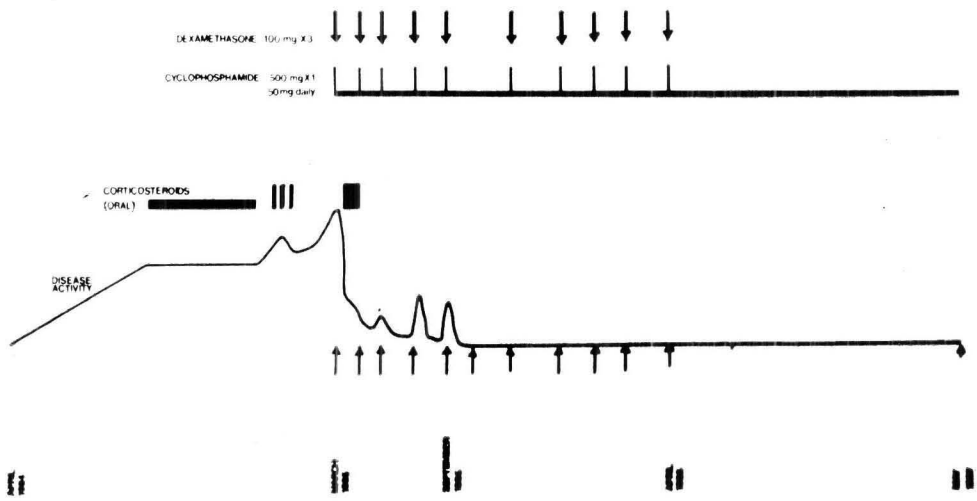

Fig. 1. Clinical course of the disease and the treatment in a pemphigus patient.

treated during their very first episode of pemphigus. Most patients had already been on corticosteroids in their usual daily regimes and had the well known side effects before being taken up for this regime. Patients less than 15 years in age were given 2 doses of dexamethasone instead of 3 and 400 mg cyclophosphamide during each DCP.

The current status of the 100 patients treated with our regime is shown in table I. Thirteen patients in this group have been lost to follow-up, and 4 have died. Of the remaining 83 patients, 76 patients are already in remission, while 7 are still having active disease. Of the 7 patients still having active disease, 2 have been taken up for this treatment only recently, 2 are having only residual oral ulcers without any skin lesions, while the remaining 3 have not been taking the treatment regularly. Of the 76 patients who are now in remission, 15 have been induced into the remission only recently (less than 6 months) and, therefore are still in phase II

Table I. Current status of pemphigus patients treated with the dexamethasone cyclophosphamide regime.

Year of starting DCP	Total number of patients treated	Number of patients with disease				Lost to follow up	Died
		Active	Remission				
		Phase I	with DCP II	Only C III	No treatment IV		
1982	4	—	—	—	3	1	—
1983	8	1	2	1	3	1	—
1984	7	—	1	1	3	1	1
1985	20	1	1	7	9	2	—
1986	30	4	5	9	7	5	—
1987	31	1	6	17	1	3	3
	100	7	15	35	26	13	4

and taking monthly DCP, 35 patients are in phase III and are now taking only 50 mg cyclophosphamide daily, while in 26 patients all the treatment has already been withdrawn (phase IV). All these patients are being followed-up for any recurrences of pemphigus lesions.

The duration of remissions has already been more than 2 years in 22 patients (maximum 4½ years). Of the 4 patients who died, 1 patient died at his home. He had taken 13 DCP but was still having active disease though it was far milder. He had not reported for several months, his death was reported to us through correspondence. The other 3 patients died in our hospital. One of them was inadvertently given an additional dose of methotrexate. He developed leucopenia (TLC 300 cells/cmm) and died the next day. The second patient died of septicemia because of uncontrolled infection, while the third died of right heart failure and bronchopneumonia. He had taken his first DCP 6 days before his death.

Of the 13 patients lost to follow-up, 1 patient belongs to Afghanistan. She had been in remission for 3 months before she left India, and there has since been no information. Six patients belong to other distant towns and found it inconvenient to come to Delhi every month. Two patients felt their disease to be too mild to justify intensive treatment with us, while in the remaining patients, recurrences of the disease during the first phase of our treatment apparently frustrated them and they opted for the routine previous methods. The duration of phase I (the time interval between the start of DCP and the onset of permanent remission) varied widely in different patients. In 11 patients, there was no recurrence of the disease ever since the first DCP, there thus being no phase I. Among the others, the duration of phase I was 1-6 months in 27 patients, 6 months to 1 year in 10 patients, 1-2 years in 18 patients, and more than 2 years in 10. The duration of phase I showed no correlation with the clinical severity of the disease or its duration before starting our regime. The skin lesions were observed to stop recurring earlier than the mucosal ulcers in almost all patients. Some patients continued to relapse with only oral ulcers for several months before going into complete remission.

Side effects

The side effects usually associated with prolonged treatment with corticosteroids and cyclophosphamide were virtually absent with this regime. Increase in weight, Cushing's type obesity, striae, acne, electrolyte disturbances, cataract, osteoporosis, hypertension, diabetes etc were not seen except when these were already present due to previous treatment with daily corticosteroids. Our patients did not require restriction of sodium or administration of potassium, calcium or anabolic hormones. A temporary rise of blood sugar level, partly due to the intravenous glucose drip was recorded in each patient, but this treatment could be given to diabetic patients also without any complications. Concomitant treatment for diabetic patients was no doubt continued. The same applied to patients having hypertension or peptic ulcers.

The chief side effect observed in these patients was increased susceptibility to infections. Secondary pyodermic infections were observed in almost all patients as long as they had ulcerated skin lesions. Some patients developed even primary pyodermas as long as they were on DCP. Less commonly, tonsillitis, pharyngitis or lung infection were also encountered. After the DCP was withdrawn, the incidence of pyogenic infections was significantly reduced. Candidiasis of the oral mucosa was another common infection prevalent in patients having oral ulcers; but this also disappeared when the mouth ulcers stopped recurring. Three patients had widespread tinea corporis. Aphthous-like, small, painful and inflamed ulcers in the mouth were also frequent during phase I of the treatment. In 4 patients, tuberculosis of the lungs

got reactivated necessitating concomittent antitubercular therapy. Throughout this period, these patients were given systemic antibiotics and oral anticandida drugs as and when required.

A mild diffuse loss of hair, generalised weakness, bone pains and lethargy for 1-5 days after the DCP, and amenorrhoea were the other side effects noticed by some patients, but none of these was serious enough to necessitate interruption of the treatment. DCP was not given to pregnant female patients, but after the completion of treatment, at least 3 of the young female patients who got married have conceived. One male patient has however, been found to be sterile though it is not known whether this sterility developed due to this regime. Sperm counts during this treatment were not undertaken.

Comments

Pemphigus is known to have high morbidity and mortality.[4] The exact rate of mortality has not been worked out because some patients may live for even 10 years or more after the onset of the disease, but every patient is considered to terminate fatally sooner or later. Before the advent of corticosteroids, mortality rates were recorded to be 90%.[5] With corticosteroids, it has become possible to prolong the life of the patient, but the disease continues to be potentially fatal in most of the cases. In addition, patients on prolonged corticosteroid therapy develop several side effects adding to the morbidity of the disease and some patients now die because of the side effects of prolonged corticosteroid therapy.[6] Immuno-suppressive drugs help to reduce the dependence on corticosteroids but the outcome of the disease has remained almost unchanged.

Against this bleak back-ground of the disease, some workers have recorded a few patients who have recovered from pemphigus in the sense that they are not getting any recurrences of the disease, even without any maintenance treatment for prolonged periods of follow-up. Such instances are few only. The recent report by Lever and Schaumburg-Lever[7] however, that early intensive treatment can lead to a complete remission in pemphigus, and that pemphigus can be considered to be a self-limiting disease, is very encouraging.

With our regime, it was possible to induce almost every pemphigus patient into a complete remission. The patients who are at present, still in phase I (having active disease) are either those who have started this treatment only recently, or those who have in fact already improved considerably except for a few oral ulcers which still keep recurring. In due course, these patients are also expected to go into complete remission. In contrast, 3 patients who have not been regularly reporting to us for DCP every month and thus have not followed our regime properly are continuing to have active disease or have shown recurrences after brief periods of remission. This emphasizes the fact that firstly the remissions induced in our patients are attributable to the treatment regime, and secondly regular DCP during this phase are essential. Intervals longer than 1 month between the DCP were not sufficient to achieve optimum results.

The second important observation was that once the patient had been induced into the remission phase, and completed the 6 months of phase II, i.e. 6 one-monthly DCP also, the remission seemed to be permanent. None of these patients has shown any tendency for reactivation of the disease. The maximum duration of remission at present is 54 months while in 22 patients the remission has already been more than 2 years. The durations of these remissions may not be so impressive at present but these patients are without even maintenance treatment and have rejoined their respective duties as normal individuals. The other patients are also showing similar trends. Though it will be necessary to have as long a follow-up as

possible in each of these patients for further substantiation, at present it can be surmised that the regime used by us is effective in inducing almost every pemphigus patient into a phase of remission which has so far shown no tendency for recurrence over prolonged periods of follow-up even after the treatment has been withdrawn completely. Whether these patients can be considered to have been cured of pemphigus is a debatable question because the minimum criteria for a cure in pemphigus have not so far been discussed. In cancer patients, a five-year relapse-free period is considered adequate, but pemphigus is a far more active disease and relapses are expected much earlier though some pemphigus patients may remain in remission for several years before they become active again. We propose, that a minimum period of two years of continuous clinical remission, supplemented with a negative test for intercellular antibodies in the blood on two occasions at least 1 year apart, should be considered adequate for the time being. These criteria can however, be modified if future experience indicates otherwise. Our data with the estimation of titres of intercellular antibodies at various stages of treatment is not yet adequate, but the autoantibodies as a rule tend to decrease and then disappear as the treatment progresses through the various phases.

The four fatalities observed in our patients could have been prevented with better cooperation on the part of the patients and better hospital care, though deaths due to unrelated causes would perhaps continue to occur.

A distinctive feature of treatment with our regime was relative freedom from side effects expected in patients treated with corticosteroids and immuno-suppressive drugs. The patients could continue to take their normal diet without restriction of calorie and salt. Diabetes mellitus, hypertension and peptic ulceration were no contra-indications. We however avoided giving it to a pregnant patient. During pregnancy, we maintained one patient on daily corticosteroids in as minimum a dose as possible. She delivered a baby having clinical blisters and intercellular antibodies in blood, but the child recovered completely. The DCP in this patient was initiated after the delivery and she also recovered. The pyogenic and candidial infections were more frequent and so was the tendency for reactivation of tuberculosis. During phase I and II, many patients developed oral candidiasis or aphthous-like ulcers which could be due to cyclophosphamide toxicity. We would, therefore, routinely prepare Tzanck smears from oral ulcers, and also look for candida in smears prepared in 10% KOH, and other organisms in Gram stained smears. A patient was considered to have active pemphigus only if the oral ulcers were large and superficial, and showed acantholytic cells in Tzanck smears. In case the patient had candidiasis or showed presence of other organisms, appropriate treatment was given concomittently. It is essential to be alert about these complications and take necessary measures.

A high dose of cyclophosphamide is also known to lead to gonadal failure, and a few of our patients have reported amenorrhoea. The possibility of gonadal failure must however be borne in mind especially in the younger patients, and it may be worthwhile to try other cytostatic drugs. A large majority of pemphigus patients however, are older and may choose to lose the gonadal function in the face of a potentially fatal disease. Patients were advised to avoid pregnancy during the treatment. After completing the treatment however, three of our younger female patients have already conceived and delivered normal babies.

Since the regime used by us was entirely arbitrary, there is plenty of scope for further modifications in the choice of drugs, their dosages and the duration of various phases of treatment. Our choice for dexamethasone was based on availability and economy. Methyl prednisolone used by other workers for a variety of other

diseases was not easily available and 200 times costlier. It may be possible to obtain equally satisfactory results with other corticosteroids. It will also be worthwhile to see if smaller dose of corticosteroids will also produce similar results. The same thing may be applicable to the use of cyclophosphamide as well and its dosages. In some earlier cases, we had used only dexamethasone pulses once a month but none of the patients went into complete remission. This suggests that combination with cyclophosphamide was essential. Two patients who were taking the DCP regularly but not the daily dose of 50 mg cyclophosphamide, also continued to have relapses till they were made to take the latter as well. This suggests that even the daily dose of cyclophosphamide was essential.

The duration of phase I was extremely variable in different patients, we therefore, tried to see if this phase can be shortened. In patients who were having severe disease and early relapses between the DCP, we tried to give DCP at 2-week intervals instead of 4 weeks to see if the remission could be induced earlier. Most of these patients however, started having severe oral candidiasis and secondary bacterial infection, creating more difficulties in their management. This approach therefore was abandoned resulting in a decline in the rate of secondary infections.

Duration of the second phase had been arbitrarily fixed by us at six months but it is essential that the patient receives at least 6 DCP at monthly intervals. Four patients who were not regular during this phase and came at longer intervals to take their DCP showed reactivation of their disease, so that they had to be reverted to phase I till they again got into complete remission. The remaining patients who continued to take regular one-monthly DCP during phase II showed no reactivation. Thus, it seems almost essential that the patient takes 6 regular one-monthly DCP during phase II. The incidence of pyogenic infections in the skin was far lower compared to phase I, though some patients did have oral aphthous-like ulcers and even candidiasis.

Like phase II, the duration of phase III had also been arbitrarily fixed to be 1 year. None of the patients in this phase had shown any reactivation of the disease. Some patients who did report back with skin lesions were found to have either primary pyoderma or dermatophytosis (possibly due to cyclophosphamide) which regressed on appropriate treatment. It is not yet certain whether it is necessary to continue this phase of treatment for full 1 year. Since none of the patients has so far shown any recurrence, it seems that this duration of phase III is adequate. In some cases however, we have withdrawn this treatment earlier than 1 year (6-9 months), to see if a shorter duration of this phase of treatment will also be adequate.

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