Dexamethasone Cyclophosphamide Pulse Therapy in Pemphigus: A Retrospective Study of Factors Influencing Phase I

Abstract

Introduction*: The introduction of dexamethasone-cyclophosphamide pulse (DCP) therapy for management of pemphigus has significantly reduced the mortality and morbidity associated with the disease. Although it is well established that phase I of DCP is the primary determinant of the duration and outcome of treatment, there are very few studies regarding factors that influence this phase of therapy*. ***Objectives****: This study was undertaken to analyze the relationship between various factors and duration of phase I.* ***Methods****: A retrospective analysis of 40 patients of pemphigus on DCP was conducted.* ***Results****: Disease severity in pemphigus significantly prolonged the duration of phase I of DCP. Other factors such as age, gender, type of disease, or presence of oral lesions were found to have no significant effect on duration of phase I.* ***Conclusion****: The observations of our study aid in addressing the concerns and expectations of pemphigus patients being treated with DCP regarding probable duration and outcome of therapy and lead to better management of the patient, and the disease.*

Keywords: *Dexamethasone cyclophosphamide pulse therapy, pemphigus, phase I, pulse therapy*

INTRODUCTION

Pemphigus is a chronic autoimmune epidermal bullous disease caused by autoantibodies directed against desmogleins and desmosomal glycoproteins expressed on the epithelial cells of skin and mucosae, resulting in acantholysis. Mortality due to pemphigus, in absence of treatment, was as high as 90-100%.[1] The introduction of corticosteroids in its management significantly decreased the mortality to 25-45%.[2] The mortality has further reduced to less than 10% with the advent of adjuvant immunosuppressive agents.[3]

Dexamethasone-cyclophosphamide pulse (DCP) therapy, first designed by Pasricha and Gupta for use in pemphigus,[4] ushered in a revolution in pemphigus management. The DCP regimen is administered in four phases.[5] In phase I, dexamethasone 100mg is given intravenously dissolved in 500 ml of 5% dextrose over three hours on three consecutive days. Cyclophosphamide 500 mg is dissolved in the same infusion on the second day. The same cycle is repeated at interval of 28 days. The patient receives daily oral cyclophosphamide 50 mg between pulses. During this phase, the patient may continue to develop recurrences in between the pulse infusions and can then be given additional treatment, either daily oral corticosteroids or additional dexamethasone pulses every 2 weeks. After the skin and mucous membrane lesions have resolved completely and additional medications have been withdrawn, the patient is considered to have entered phase II. During phase II, the patient continues to receive pulses at 28 days intervals for 9 months along with 50 mg cyclophosphamide orally daily. In phase III, monthly pulses are stopped and cyclophosphamide 50 mg daily is continued for another 9 months. After this, the patient moves to phase IV, where treatment for pemphigus is withdrawn completely and the patient is followed up lifelong to look for any relapse. In case of development of any new lesion during phases II‑IV, the patient is restarted on phase I. DCP is a safe and effective therapeutic regimen and has made cure or permanent remission possible in more than 90% patients when the regimen is strictly followed.[6,7]

It is evident that phase I of DCP is variable from patient to patient and, as such, the primary determinant of the total duration of treatment required in an individual patient. In our experience, it was found that the

length of phase I varied from as short as 3 months to as long as nearly 20 months. Therefore, this study was undertaken to delineate the factors that influence the duration of phase I, which seemingly have a direct bearing on the overall prognosis in a patient of pemphigus put on DCP.

MATERIAL AND METHODS

A retrospective study was conducted amongst 40 patients with a diagnosis of pemphigus who had undergone treatment with DCP between 2007 and 2015 at the Department of Dermatology, Assam Medical College & Hospital, Dibrugarh. The study observations are based upon a retrospective analysis of clinical data of these patients collected over a period of 7 years. Patient photographs were not used nor could any patient be identified from any of the data provided in this article. Hence, no ethical clearance was sought.

The data recorded for all patients included a detailed history (duration of disease, the type and distribution of lesions, associated symptoms and other diseases, course of illness and drug history) and a thorough clinical examination at first visit and on follow up. The diagnosis was made on clinical grounds and confirmed by positive Tzanck smear, supplemented by histopathology and direct immunofluorescence in almost all cases. The clinical severity of disease was recorded for all patients based on the number of skin lesions and disease was classified as mild (<15 skin blisters or erosions), moderate (15 to 30 skin blisters or erosions) and severe (>30 skin blisters or erosions or extensive confluent areas of erosion). Routine investigations such as complete haemogram, erythrocyte sedimentation rate, fasting and post-prandial blood glucose levels, liver and renal function tests, serum electrolytes, urine analysis, baseline ECG, chest radiograph and ophthalmological examination for cataract and glaucoma were performed in all patients and results were duly recorded.

The study patients were administered the modified DCP treatment regimen.[5] Any concurrent illness and/or infections were treated appropriately without discontinuing the DCP therapy. Kaplan-Meier survival analysis was done on the data of those patients who had successfully completed phase I of DCP, and the p value was calculated using chi-square test.

RESULTS & OBSERVATIONS

The age of patients recruited for the study ranged from a minimum of 16 years to a maximum of 65 years with the mean being 40.67 years (Table 1). Almost a third of them were in their 4th decade of life; and close to three-fourth in the age group 31-60 years. Females (n=24; 60%) outnumbered males (n=16; 40%) by a ratio of 3:2.

Table 1: Age distribution of patients

Age group (in years)	Number (N)	Percentage (%)
0-10	0	0
11-20	5	12.5
21-30	4	10
31-40	12	30
41-50	9	22.5
51-60	8	20
61-70	2	5
71-80	0	0
Total	40	100

The overwhelming majority (n=29; 72.5%) of patients had pemphigus vulgaris while there were 10 (25%) cases of pemphigus foliaceus and a solitary case (2.5%) of pemphigus vegetans. Oral lesions were present in as many as 23 (57.5%) of the patients. The **a**verage duration of disease at presentation was 7.01 months,

with a maximum duration of 60 months and minimum of 0.1 months. The average duration of Phase I of DCP was 6.72 months, with a maximum duration of 20 months and a minimum of 3 months.

Age (Fig 1) and gender (Fig 2) of the patient were not found to have appreciable effect on duration of phase I of DCP; p value of 0.225 and 0.666 respectively (p value > 0.05). Patients with pemphigus foliaceus (PF) took slightly longer than those with pemphigus vulgaris (PV) to clear phase I but the difference was statistically insignificant; p value > 0.05 (Fig 3). Oral lesions are known to be recalcitrant to treatment. However, in the present study, no significant difference was found in the duration of phase I between patients with oral lesions and those without; p value > 0.05 (Fig 4). On the other hand, disease severity was found to significantly influence the duration of phase I; p value 0.00 (Fig 5).

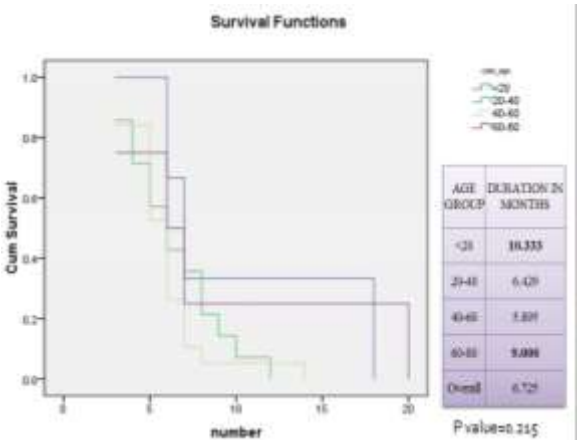

FIGURE 1: Relation between age and duration of phase I

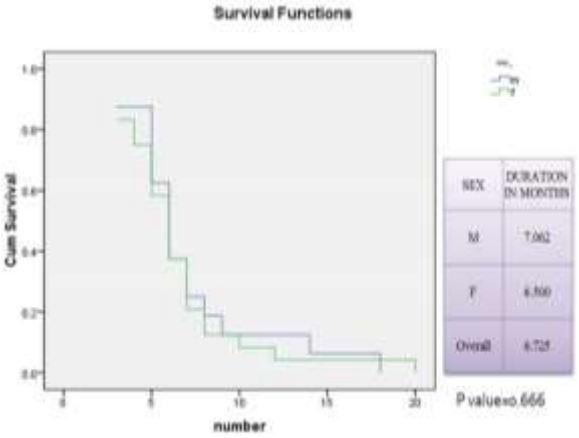

FIGURE 2: Relation between sex and duration of phase I

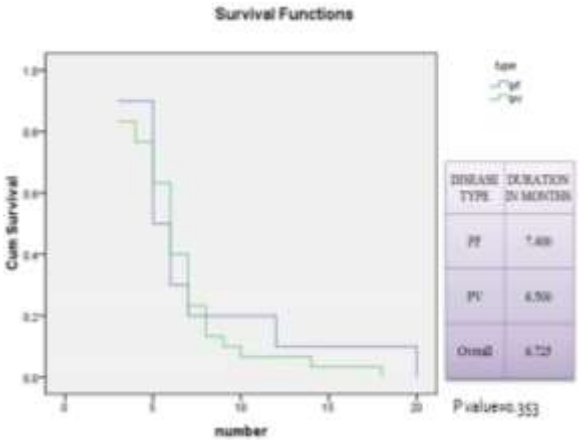

FIGURE 3: Relation between disease type and duration of phase I

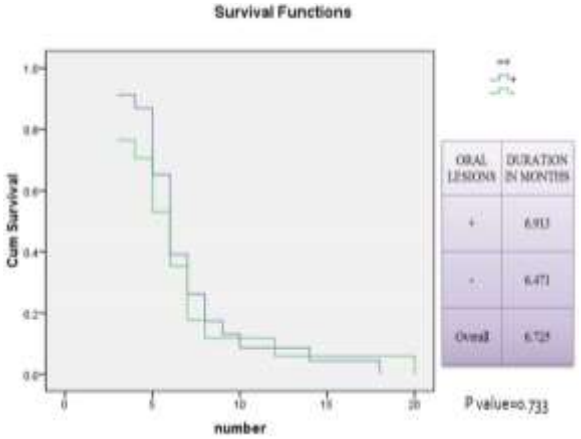

FIGURE 4: Relation between oral lesion and duration of DCP phase I

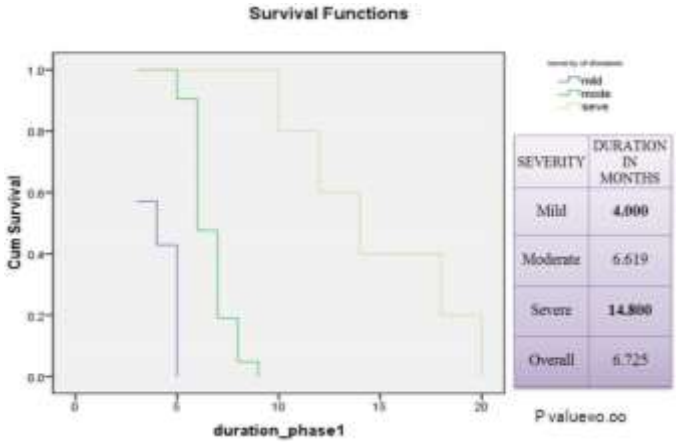

FIGURE 5: Relation between disease severity and duration of DCP phase I

DISCUSSION

DCP is a widely used therapy in patients with pemphigus and other dermatological disorders. It is, however, surprising that there is only a single Indian study[8] that has attempted to assess the factors that affect the duration of phase I of DCP and none from our neck of the woods. This study was undertaken to fill that information lacuna.

As many as thirty six (90%) of the 40 patients enrolled in our study completed phase I of DCP with 10 or less pulses. This is comparable to a study by Pasricha *et al*[5] where 83.7% patients required up to nine pulses in phase I. Similarly, eighty four (85.7%) of the 98 patients completed phase I within 10 months in a study by Chitra *et al*.[8]

The age, gender, type of disease, or presence of oral lesions were found to have no significant effect on duration of phase I of DCP in our study. We, however, found that the severity of pemphigus correlated with the duration of phase I of DCP. This is in accordance with the findings of the study done by Chitra *et al.*[8] Kanwar *et al.*[9,10] had reported in their series that the response to pulse therapy was faster in mild disease and that severe disease entails more number of pulses as well as higher doses of interval oral corticosteroids. These results are similar to those of our study but are contrary to the observations made by Rao *et al.*,[11] who did not find the duration of phase I of DCP to correspond with the severity, extent, duration or grading of pemphigus.

CONCLUSION

The severity of pemphigus is a clinically important and statistically significant determinant of duration of phase I of DCP. The findings from a larger study with greater sample size will provide more detailed understanding of the interplay between various other patient and disease related factors responsible for affecting the duration of phase I of DCP. This will be pivotal in addressing the concerns and expectations of pemphigus patients being treated with DCP regarding probable duration and outcome of therapy.

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Ethical clearance: The study is based upon a retrospective analysis of clinical data of patients. Patient photographs were not used nor could any patient be identified from any of the data provided in this article. Hence, ethical clearance was not warranted and none was sought.

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