

Cyclophosphamide pulse therapy for pemphigus: report of seven cases*

*Pulsoterapia com ciclofosfamida nos pênfigos: relato de sete casos**

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Abstract: The efficacy of cyclophosphamide pulse therapy was evaluated in pemphigus vulgaris (2 males and 4 females aged 34 to 47 years) and in a 56-year-old male with pemphigus foliaceus. The inclusion criteria for pulse therapy were: prednisone failure, important side effects, recurrence of disease during the withdrawal and maintenance oral prednisone 40 mg daily. In one case (5 pulses), the maintenance dose of prednisone was reduced to 10 mg; in another case (9 pulses), to 20 mg; in 2 cases (10 pulses), to 20 mg; in 1 case (9 pulses), to 30 mg; in 1 case (7 pulses), no prednisone was required; and in 1 case, the cyclophosphamide was interrupted due to leukopenia.

Keywords: Cyclophosphamide; Pemphigus; Pulse.

Resumo: A eficácia da pulsoterapia com ciclofosfamida foi avaliada no pênfigo vulgar (dois homens e quatro mulheres entre 34 e 47 anos) e em um homem de 56 anos com pênfigo foliáceo. Os critérios de inclusão para pulsoterapia foram: não controle com prednisona, efeitos colaterais importantes, recorrência da doença nas tentativas de redução da prednisona e dose de manutenção $\geq 40\text{mg}/\text{dia}$. Em um caso (cinco pulsos) a dose de manutenção da prednisona foi reduzida para 10mg; em um caso (nove pulsos), para 20mg; em dois casos (10 pulsos), para 20mg; em um caso (nove pulsos), para 30mg; em um caso (sete pulsos) foi zerada; em um caso a ciclofosfamida foi suspensa por leucopenia.

Palavras-chave: Ciclofosfamida; Pênfigo; Pulso.

INTRODUCTION

Corticoids are the foundation of therapeutics for pemphigus, however their side effects have led to a constant search for alternatives. Cyclophosphamide pulse therapy¹ is based on studies into lupus nephritis, Wegener's granulomatosis and Behçet's disease. These have suggested that it has greater efficacy when compared to exclusive pulse therapy with oral and venous corticoids; furthermore, it triggers fewer side effects than oral cyclophosphamide; it is accomplished with or without pulse intravenous corticoids.^{2,3} In either case, a lower dose of cyclophosphamide or oral corticoids is administered between the cycles. The concomitant pulse - cyclophosphamide and corticosteroid^{4,5} - leads to complete remission in 37% and mortality in 3% of cases.^{6,7}

CASE REPORTS

The cases were studied at the University Hospital Clementino Fraga Filho - from 1998 to 2004 - after histopathological confirmation in samples of skin and/or oral mucous membrane.

1. Prednisone

1.1. dose: 1 mg/kg/day; max.: 120 mg/day/orally

● period: 4, 6, 10 weeks

● relative contraindications to the corticotherapy: peptic ulcer, diabetes mellitus, cataracts, osteoporosis, arterial hypertension, tuberculosis, obesity, glaucoma and advanced age

● limited pictures of pemphigus vulgaris/foliaceus

● exclusive mucous lesions in pemphigus vulgaris

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1.2. dose: 2 mg/kg/day; max.: 120 mg/day/orally

- period: 4, 6, 10 weeks
- extensive picture (skin + mucous membranes) of pemphigus vulgaris
- progressive cutaneous disease (pemphigus vulgaris and pemphigus foliaceus)

1.3. withdrawal sequence

1st stage: 10 mg orally every 10 days

2nd stage: a dose of 20 mg/days, maintained for six months

3rd stage: 10 mg (six months) → 5 mg (six months) → 2.5 mg (six months). Interruption after one year without lesions.

2. Inclusion criteria for cyclophosphamide pulse therapy: resistance to control with prednisone; weight gain and emotional lability leading to refusal of corticoid; psychosis, aseptic necrosis of the femur head, severe arterial hypertension, uncontrolled diabetes mellitus; recurrence of the disease following attempts to reduce the drug; maintenance dose of prednisone 40 mg/day; absence of pregnancy; and inefficacy of azathioprine.

2.1. blood count, biochemistry and urine analysis before the pulse, every three weeks

2.2. dose

600mg/m² of corporal surface diluted in 200 ml of 5% glucose serum, slowly intravenous during one hour

- Kytril - 3 mg in 20 ml of 0.9% physiologic serum I.V., during 5 min or
- Zofran - 8 mg in 20 ml 0.9% physiologic serum I.V. for 5 min before cyclophosphamide application;
- Vigorous oral hydration 24 hours before and 36 hours after the application
- criteria for interruption: leukopenia (<3,000 leukocytes), thrombocytopenia (<100,000 platelets) and red blood cells in urine analysis (>10), infections;

Case 1

Case 1 - LFS, 40 years old, female, RJ; five years with pemphigus vulgaris (skin and mucous membranes). Hypercholesterolemia and incipient cataract.

Prednisone (2 mg/kg/day/orally) for two months without control of the picture; five cyclophosphamide puls → maintenance of 10 mg/day. Follow-up until 2004; without lesions in the last six months.⁸

Case 2

FDN, 47 years old, male, RJ; 15-year history of pemphigus vulgaris (skin and mucous membranes).

Subcapsular cataract and arterial hypertension.

Prednisone (2 mg/kg/day/orally), → 40 mg/day still with lesions; addition of azathioprine (2 mg/kg/day/orally) without improvement of the picture; interruption of azathioprine; introduced chloroquine (300 mg/day/orally) without result; interruption; nine cyclophosphamide pulses → 20 mg/day. Follow-up until 2004; the last six months without lesions.⁸

Case 3

SL, 40 years old, female, RJ; four-year history of pemphigus vulgaris (skin and mucous membranes). Arterial hypertension.

Prednisone (2 mg/kg/day/orally) and azathioprine (2 mg/kg/day/orally) without control of picture; interruption of azathioprine; nine cyclophosphamide pulses → maintenance of 30 mg/day; she presented microscopic hematuria. Follow-up until 2004; on average three lesions in the oral mucous membrane; local infiltration of corticoid with control of the picture; to 20 mg/day.⁸

Case 4

KSM, 34 years, female, RJ; one-year history of pemphigus vulgaris (skin and mucous membranes).

Prednisone (2 mg/kg/day/orally) for 30 days with regression and recurrence; addition of azathioprine (2 mg/kg/day/orally); it was interrupted because the maintenance dose of prednisone was kept at 90 mg/day; 10 cyclophosphamide pulses to prednisone 20 mg/day/orally with minimal lesions in the superior gum. The complications were microscopic hematuria, amenorrhea and cystitis. Follow-up until 2004, with three lesions in the superior gum; intralesional corticoid infiltration, one lesion persisting.⁸

Case 5

JMS, 56 years, male, RJ; six-year history of pemphigus foliaceus.

Prednisone (1 mg/kg/day/orally) and chloroquine (300 mg/day/orally) → maintenance of prednisone at 40 mg/day; chloroquine was interrupted; 10 cyclophosphamide pulses, to 20 mg/day/orally prednisone. Follow-up until 1999, without lesions.⁸

Case 6

FPM, 42 years old, female, RJ; two-year history of pemphigus vulgaris (skin and mucous membranes).

She developed a major gastric intolerance to the corticoid. Concomitant pulses of dexamethasone and cyclophosphamide were administered. Electrolytes, amylase, stool's examination ECG and ophthalmologic exam before the dexamethasone pulse; in which 100 mg dexamethasone was diluted in 500 ml of 5% glucose serum, flowing for two hours every day for three days,

total of three pulses. In the second pulse, the patient presented leukopenia, whereupon the cyclophosphamide was interrupted. Since the picture was extensive, prednisone was started (2 mg/kg/day/orally). In the tenth week (a pulse of dexamethasone + prednisone), still without control of the picture; treatment with azathioprine was begun (2 mg/kg/day/orally). In the third week of azathioprine and the seventh dexamethasone pulse, prednisone was progressively withdrawn. At a dosage of 70 mg/day/ orally, there was a worsening of the lesions. Azathioprine was interrupted due to discontinuity in its availability. Twelve dexamethasone pulses were completed with \rightarrow 30 mg/day of prednisone. In the follow-up until 2004, there were still three lesions in the oral mucous membrane and five lesions in the skin.⁸

Case 7

NSP, 47 years, male, RJ; nine-year history of pemphigus vulgaris (skin and mucous membranes). Aseptic necrosis of the femur head (bilateral).

Prednisone (2 mg/kg/day/orally) was administered with remission of the picture for ten months. Following recurrence of the picture; prednisone with azathioprine (2 mg/kg/day/orally) were reinitiated with a renewed remission that lasted a year. After further recurrence, seven cyclophosphamide pulses were administered, eventually with the appearance of only two to three mucous lesions controlled with topical triamcinolone and clobetasol. Follow-up until 2004, patient was without prednisone use.⁸

DISCUSSION

Cyclophosphamide is a potent alkylating agent that, in small doses causes a decrease in the cellularity of the lymphoid organs, without affecting the hematopoietic cells. In high doses it is selectively toxic for B lymphocytes (Chart 1). In pulse form, it carries a minor potential for malignancy and infertility.⁷ The patients were advised about the risks of the medication, however there was agreement (because of having a constituted family, lack of active sexual life, and due to the suffering caused by the disease). In oncological practice, the dosage is greater (> 50 mg/kg); for auto-

immune diseases, such as lupus nephritis it is usually less than 20 mg/kg per dose; in pemphigus, from 500 mg to 1g/m² of corporal surface.³ The number of pulses is variable: 14 to 48,⁴ with a maximum of 15.⁶

Previously had the main author studied five cases (Table 1): from three to nine pulses were employed; two patients improved, obtaining of prednisone maintenance dose. In the cases of Pandya,³ the prednisone doses and the number of pulses were similar, however there was no follow-up (Table 1). In the present series, six cases improved with reduction of the dosage to 30 mg/day (one case), 20 mg/day (three cases), 10 mg/day (one case), none prednisone (one case). Oral cyclophosphamide was not used in the intervals due to a lack of the drug on the market.

In cases 3 and 4 there was persistent hematuria with a normal cystoscopy and biopsy of the bladder; 24-hour protein, creatinine clearance, urea, and creatinine within normal limits, excluded nephropathy. The therapeutic regimen was kept. In case 6, the option was to interrupt the pulse with cyclophosphamide due to leukopenia, while maintaining dexamethasone.

Corticoids are not usually administered in the intervals between pulses, unless there is recurrence of the lesions before the next pulse (from two to four weeks).⁶ Daily doses of 30-40 mg prednisone are recommended during these intervals. In the studied cases here, that were submitted to pulse therapy with only cyclophosphamide, it was possible to reach a lower maintenance dose. In the literature, prolonged persistence of the oral lesions is reported, as well as the hypothesis that they are an expression of the disease activity. The authors' observations were similar.

Pulse therapy, usually with methylprednisolone, has been used to control acute exacerbations of serious immunological diseases. The Indian authors' innovation consists of the association of dexamethasone / cyclophosphamide, dividing the treatment into four phases:⁵

1st phase: rapid healing of the lesions with pulses at intervals from two to four weeks and oral cyclophosphamide (50 mg) between the pulses;

2nd phase: progressively milder recurrences;

3rd phase: after six months of remission, inter-

CHART 1: Side effects of cyclophosphamide

Frequent	Rare
Nausea, vomiting	Hyperpigmentation
Alopecia	Fibrosis of the bladder and lungs
Amenorrhea, oligospermia, azoospermia	Altered hepatic function
Leukopenia, thrombocytopenia	Mucous ulcers
Hemorrhagic cystitis	Myocarditis
	Malignant neoplasias of the skin and bladder
	Non-Hodgkin's lymphoma

TABLE 1: Cyclophosphamide pulse therapy for the treatment of pemphigus

Author, year	N° of cases		Dose of prednisone/day	N° of pulses	Follow-up (months)	Partial remission Maintenance dose	Without partial remission	Side effects	Mortality (n° / %)
	PV	PF							
Pandya, 1992	1		40mg	7	-	5mg		Nausea	N
	1		80mg	11	-	-		Nausea, vomiting	N
Wanke, 1994	1		60mg	3	60	5mg		N	N
	1		60mg	9	7		Y	N	N
	1		80mg	6	4		Y	N	N
	1		80mg	5	3		Y	N	N
	1		90mg	6	4	40mg		N	N

Key:

- : not given

PV: pemphigus vulgaris

Y: yes

PF: pemphigus foliaceus

N: no

ruption of the pulses, but with oral cyclophosphamide;

4th phase: after a year of oral cyclophosphamide, interruption of all treatment.

In case 6, which was extremely severe, recurrence of the lesions was observed before each pulse with dexamethasone,⁴ as well as no sparing action of azathioprine. It is to be hoped that the relapses will be interrupted after a varying number of pulses.⁴ The natural history of the disease suggests that two years without treatment and without disease activity, should be criteria for cure, although the longer the follow-up the greater the assurance.⁵

Here the following phases were established:

1st phase: complete remission of skin lesions and partial remission of oral mucous membrane

lesions (three active lesions);

2nd phase: of prednisone down to 20 mg/day/orally;

3rd phase: interruption of pulse therapy;

4th phase: after a remission of six months, of prednisone.⁸

With regard to azathioprine, used in a dosage of 2 mg/kg/day/orally, it should be remembered that dosages from 3.5 to 4.5 mg/kg/day/orally are recommended and considered more effective.⁹ Since they may be accompanied by significant gastrointestinal side effects and cytopenias, dosages of over 2 mg/kg/day/orally were not used.

Treatment with cyclophosphamide pulse therapy was shown to be a safe and effective alternative in the studied cases of pemphigus of difficult control. □

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