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The Safety of Intravenous Cyclophosphamide in the Treatment of Rheumatic Diseases

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Background. The therapeutic effects of cyclophosphamide (CP) in the treatment of systemic rheumatic diseases are related to its immune suppressive activity. However effective, the application of CP is restricted due to multiple adverse effects.
Objectives. This retrospective study was conducted to determine the frequency of adverse effects attributed to CP toxicity.
Material and Methods. The study involved 65 patients (17 male; 48 female) receiving intravenous CP between October 2007 and December 2010. The mean age at onset was 51.2 years (range 19–77 years). The most common diagnoses were systemic sclerosis (20), systemic lupus erythematosus (13) and vasculitis (13). The indications for treatment with CP were interstitial lung disease in the course of systemic diseases (33), vasculitis (24), glomerulonephritis (5) and changes in the central nervous system (3). The patients were administered 400–1000 mg CP in intravenous infusions at 2–16 week intervals, with the addition of sodium 2-sulfanylethanesulfonate (mesna) before and after each pulse.
Results. Out of 65 patients 40 (60%) reported adverse effects: infections in 24 (37%), nausea in 19 (29%), vomiting in 11 (17%), abdominal pain in 7 (11%) and pancytopenia in one, leading to cessation of the therapy. No association was found between the frequency of side effects and the treatment duration ($p = 0.632$), age ($p = 0.852$), diagnosis ($p = 0.171$) or nominal dose ($p = 0.321$).
Conclusions. As knowledge about CP continues to increase, this medication remains a safe way to treat many rheumatic diseases (**Adv Clin Exp Med 2016, 25, 3, 479–484**).

Key words: rheumatic diseases, adverse effects, cyclophosphamide.

Cyclophosphamide (CP) is a cytotoxic agent belonging to the group of alkylating drugs and it is used in the treatment of chronic systemic rheumatic diseases [1]. The application of this drug is limited because of multiple adverse effects. Despite this, and despite advances in the treatment of rheumatic diseases, CP has been a widely used drug for more than three decades and its effectiveness has been already proven.

This paper is a retrospective analysis of the early adverse effects which occur as a result of the use of intravenous infusions of CP in patients with selected rheumatic diseases.

CP has an immunosuppressive, cytotoxic and anti-inflammatory effect. It can be administered both intravenously and orally in an inactive cytostatic form. The oral dose is usually administered daily, but in the intravenous form it is supplied as a pulse every three or four weeks. No significant differences in the metabolism or concentration of metabolites have been observed between the intravenous and oral forms. CP is metabolized in the liver by cytochrome P450 enzymes to active molecules which have the ability to penetrate many types of cells [2].

Inside the cells they undergo further transformations, acquiring alkylating properties. The ac-

tive metabolites of this agent react with DNA and cause fragmentation of the DNA. This process interferes with DNA synthesis, the transcription and translation processes and results in the death of the cell. CP works in all phases of the cell cycle. It inhibits both T- and B-lymphocyte proliferation and reduces the synthesis of the antibodies that are produced by these lymphocytes. This mechanism is what makes CP useful in the treatment of autoimmune diseases; the extent of the effects varies depending on the dose, the length of the therapy and the current state of the patient's immune system. CP and its metabolites are mainly excreted with the urine [3, 4].

The primary indications for the use of CP are chronic systemic rheumatic diseases. In rheumatology, this medication is mostly applied in glomerulonephritis (mainly in the course of systemic lupus erythematosus), primary or secondary vasculitis (especially when it is accompanied by skin ulceration), polymyositis that is resistant to high doses of corticosteroids, interstitial lung disease (for example in the course of systemic sclerosis), pulmonary hypertension in systemic sclerosis, in the so-called catastrophic antiphospholipid syndrome or amyloidosis [5]. One of the absolute indications for the administration of CP is central nervous system involvement in the course of systemic lupus erythematosus. In addition, CP is often used as second-line therapy when other drugs are ineffective [6–8].

Although CP is a drug with good and proven efficacy, its use is very limited due to the numerous adverse effects; CP has a significant short- and long-term toxicity. The most common adverse reactions are marrow suppression (pancytopenia, leucopenia, thrombocytopenia), enhanced susceptibility to infections, hyponatremia, gonadal dysfunction, hemorrhagic cystitis, increased risk of developing malignancies, gastrointestinal disorders (vomiting, constipation, diarrhea) [9–11].

Material and Methods

The sample of patients analyzed in this study consisted of 65 patients (17 men, 47 women) who were treated with intravenous CP pulses at the Department of Rheumatology and Internal Diseases, Wroclaw Medical University (Poland) from October 2007 to December 2010. At the end of the study 55 patients had already finished CP therapy and 10 patients were still continuing the treatment. The average age of the patients at the start of the treatment was 51.2 years (range: 19 to 77); 46 years for men (10 men were under 50 and 7 over 50 years old) and 54 for women (17 women were under 50 and 31 over 50 years old). The most common diagnoses were systemic sclerosis (30.8%), systemic lupus erythematosus and vasculitis (both 20%) (Table 1).

Among the patients who were observed in this study, the indications for the use of CP were interstitial lung disease in the course of systemic diseases (33 patients), vasculitis (24 patients), glomerulonephritis (five patients) and changes in the central nervous system (CNS) (three patients) (Table 2). The group of patients with vasculitis consisted of patients with primary vasculitis of the medium and small blood vessels. There were six patients with *polyarteritis nodosa*, six patients with granulomatosis with *polyangiitis* and one patient with eosinophilic granulomatosis with *polyangiitis*. Patients suffering from vascular CNS damage which was confirmed by computer tomography (CT) or magnetic resonance imaging (MRI), and patients with psychiatric or neurological symptoms related to the underlying disease were grouped together and described as patients with changes in the CNS. There was also a group of five patients with glomerulonephritis, consisting of three patients suffering from lupus nephritis, one patient

Table 1. Characteristics of patients with each diagnosis

Main diagnosis:	No. of patients (women):	Percentage (% women):
Systemic sclerosis	20; (15)	30.8; (31.3)
SLE*	13; (12)	20; (25)
Vasculitis	13; (8)	20; (17.7)
RA*	9; (4)	13.8; (8.3)
MCTD*	5; (5)	7.7; (10.4)
PM*/DM*	5; (4)	7.7; (8.3)
Total	65; (48)	100%

* SLE – systemic lupus erythematosus; RA – rheumatoid arthritis; MCTD – mixed connective tissue disease; PM – polymyositis; DM – dermatomyositis.

Table 2. Clinical indications for CP

Indication:	No. of patients (%):
ILD*	33 (50.8)
Vasculitis	24 (36.9)
Glomerulonephritis	5 (7.7)
Changes in CNS*	3 (4.6)
Total:	65

* ILD – interstitial lung disease; CNS – central nervous system.

with necrotizing glomerulonephritis in the course of granulomatosis with polyangiitis and one more patient with glomerulonephritis in the course of mixed connective tissue disease.

All the patients were treated with intravenous infusions of CP during hospitalizations at average intervals of 4 weeks (ranging from 2 to 16 weeks). Each patient underwent blood tests (ESR, CRP, ALT, AST, serum creatinine, serum uric acid, eGFR, Na^+, K^+, TSH, glucose) and urinalysis. Depending on the clinical status additional tests were performed before or after the administration of CP, including imaging tests or microbiological cultures. Each patient received on average six intravenous infusions of CP (ranging from one to 20) at a dose of 400–1000 mg, with 2-mercaptoethane sulfonate Na solution (*mesna*) given before and after every infusion of CP. Each CP infusion lasted over one hour. The dosage of CP depended on the body surface (on average 422 mg per square meter). The average total dose of the drug administered was 4850 mg (from 600 mg to 14,400 mg). All the patients who had been admitted to CP therapy used varying doses of glucocorticoids. The average duration of the treatment was 216 days (from 19 to 667 days). There were seven patients who received only one dose of CP. Four of them finished their therapy after this one dose (two patients continued CP therapy in other centers, one patient did not agree to further treatment, one patient experienced pancytopenia). Three other patients were still continuing their treatment after the close of the study.

The goal of this paper was the assessment of early adverse effects associated with the administration of CP. No late complications (for example fertility disorders or increased risk of cancer) were taken into account [12, 13].

The statistical analysis included the Mann-Whitney *U* test and Student's *t*-test (to compare mean values) and the χ^2 test (to test the independence of nominal variables). The analysis was performed using STATISTICA software v. 10.0. The threshold of statistical significance was set at $p < 0.05$.

Results

Among the study participants, 40 patients (60% of the whole study group) had at least one adverse effect. The adverse effects were experienced by seven men (40% of all the men in the study) and 33 women (70% of the women). There was no statistically significant relationship between the occurrence of early adverse effects and the patient's sex ($p = 0.08$), the nominal dose administered ($p = 0.321$), the treatment duration ($p = 0.632$), the patient's age ($p = 0.852$) or the diagnosis ($p = 0.171$).

The most common adverse effects were infections (in 24 patients, comprising 37% of all the patients in the study), nausea (in 19, or 29%), vomiting (in 11, constituting 17%) and abdominal pain (in seven, i.e., 11%). Three patients experienced anemia (hemoglobin < 10 g/dL, observed during 4–6 hospitalizations); one patient had leukopenia (leukocytes $< 4 \times 10^9$/L, observed during four consecutive hospitalizations); and one patient had pancytopenia (hemoglobin < 10 g/dL, leukocytes $< 4 \times 10^9$/L, lymphocytes $< 1.5 \times 10^9$/L, blood platelets $< 150 \times 10^9$/L), which led to discontinuation of CP therapy. Three patients had hemorrhagic cystitis of the 1st degree according to the classification proposed by Droller et al., reproduced in Table 3 [14]. Detailed data on the adverse effects occurring during the treatment are presented in Table 4.

The following diseases were considered infections: skin infections (seven patients), inflammation of the upper respiratory tract (six patients),

Table 3. The classification of hemorrhagic cystitis proposed by Droller et al. [14]

0	No symptoms of bladder irritability or hemorrhage
1	Microscopic hematuria
2	Macroscopic hematuria
3	Macroscopic hematuria with small clots
4	Massive macroscopic hematuria requiring instrumentation for clot evacuation and/or causing urinary obstruction

Table 4. The frequency of adverse effects

Adverse effects	No. of patients
Infections	24
Nausea	19
Vomiting	11
Abdominal pain	7
Anemia	3
Hemorrhagic cystitis	3
Allergic reactions	2
Increase in transaminases	2
Diarrhea	1
Leucopenia	1
Pancytopenia	1

Table 5. Characteristics of the various infections experienced by the study group

Infections	No. of patients (% of all patients)
Skin infection	7 (11)
Inflammation of the upper respiratory tract	6 (9)
Urinary tract infection	5 (8)
Inflammation of the lower respiratory tract	3 (5)
Herpes zoster infection	2 (3)
Infectious arthritis	1 (2)

Table 6. Adverse effects in relation to the diagnoses

Main diagnosis	Adverse effects		
	no. of patients	% of all patients with adverse effects	% of patients with this diagnosis
Systemic sclerosis	14	35	70
SLE*	8	20	62
Vasculitis	8	20	62
PM*/DM*	5	12.5	100
RA*	3	7.5	33
MCTD*	2	5	40
Total:	40	100	

* PM – polymyositis; DM – dermatomyositis; RA – rheumatoid arthritis; SLE – systemic lupus erythematosus; MCTD – mixed connective tissue disease.

urinary tract infections (five patients), inflammation of the lower respiratory tract (three patients), herpes zoster infection (two patients) and infectious arthritis (one patient) (Table 5). *Staphyloccocus aureus* was the etiological factor in the case of infectious arthritis and all of the skin infections. It was not possible to identify the etiological factors for the upper and lower respiratory tract infections. All three patients with an inflammation of the lower respiratory tract were treated with broad spectrum antibiotics with good clinical effects. There was an increase in serum transaminases (< 3 × the upper limit of normal) in two patients (after the 2nd and 3rd infusions).

Each of the five patients with polymyositis/ /dermatomyositis (PM/DM) had adverse effects. Adverse reactions also occurred in 14 patients suffering from systemic sclerosis, which comprised 70% of all the patients with this disease who were considered in this study. Among the patients suffering from systemic lupus erythematosus (SLE) or vasculitis, 62% reported adverse effects (Table 6).

Table 7. Mean values of selected laboratory results before and after CP treatment

	Before	After	p-value
ESR [mm/h]	36.06	25.43	0.002
CRP [mg/L]	27.33	12.46	0.049
Lymphocytes [× 10^9/L]	1.64	1.35	0.005
Neutrophils [× 10^9/L]	6.91	7.11	0.840
ALT [IU/L]	32.18	27.12	0.191
AST [IU/L]	33.26	27.17	0.018
Hemoglobin [g/dL]	12.53	13.01	0.025
Serum creatinine [mg/dL]	1.02	1.01	0.626
Platelets [× 10^9/L]	287.37	267.66	0.043

The mean values of ESR and CRP after the treatment were significantly lower ($p = 0.002$ and $p = 0.049$, respectively). The mean values of lymphocytes ($p = 0.005$) and AST ($p = 0.018$) were also at a lower level at the end of the study period. The mean values of hemoglobin ($p = 0.025$) and platelets ($p = 0.043$) were higher. There were no statistically significant changes after the treatment in the mean values of neutrophils ($p = 0.840$), serum creatinine ($p = 0.626$) or ALT ($p = 0.191$) (Table 7).

Discussion

The patients considered in this study were treated with CP in order to stop or slow down disease progression or in order to prevent serious organ complications. The most important factors limiting the applicability of CP are adverse effects. As described in previous studies, the most common early adverse effects were nausea, vomiting and various infections [15, 16]. All the patients who experienced nausea or vomiting were treated with standard doses of ondansetron in oral or intravenous form, which resulted in relief of the symptoms [17]. The frequency of infections was 37%, which is comparable to the frequency reported in other studies [18, 19]. No patient had serious enough infections to require cessation of the therapy, although such situations have been described in the literature [20]. This was a result of an insightful search for possible sources of infection before administering CP and the use of appropriate preventive therapy when infections occurred.

It has been proven in previous studies that *mesna* significantly reduces the frequency of hematuria and hemorrhagic cystitis after the use of CP, while the effectiveness of the therapy remains on the same level [21–25]. In the present study, however, three patients experienced hemorrhagic cystitis despite the use of *mesna*, although this did not necessitate stopping the therapy.

So far, no correlation has been noted between the patients' sex and either the adverse effects or the effectiveness of CP therapy [26]. In this study there was no statistically significant relationship between the occurrence of early adverse effects and the patients' sex, but early adverse effects caused by CP were observed more frequently among the women than among the men. However, hormonal--sexual complications (such as menstrual disorders and early menopause) were not evaluated in the present study. Perhaps the relationship between early adverse effects and the patients' sex is associated with the higher prevalence of certain diseases among women, or with more severe disease than among men, rather than being directly related to the use of CP [27]. This issue surely requires further study.

As described in previous studies, no statistically significant relationships were found between adverse effects and the nominal dose or the duration of the therapy [28, 29]. Currently, there are some papers which describe a comparable frequency of adverse effects from the use of CP irrespective of the mode of administration [30], but comparing the use of oral or intravenous cyclophosphamide was not a goal of this paper.

As in most other studies, this study confirmed that the occurrence of adverse effects serious enough to lead to the discontinuation of CP treatment is relatively rare [31, 32]. In the present study only one patient discontinued the therapy because of pancytopenia. If adverse effects like nausea, vomiting, hemorrhagic cystitis or infections occur due to the use of CP, they are usually not sufficiently serious to stop the therapy [33].

As knowledge about CP increases, this drug remains a safe treatment for many rheumatic diseases. When using CP the risk of adverse effects should not be forgotten, but it is a therapy of proven efficacy, particularly for patients with severe systemic diseases or conditions that are refractory to other treatment [34–36].

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