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Urotoxicity and safety data of low-dose intravenous cyclophosphamide therapy for rheumatic diseases: A Single-Center retrospective cohort study

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Abstract

Despite its effectiveness in rheumatic diseases, cyclophosphamide (CYC) treatment should be used with caution due to its side effects. CYC is thought to pose a risk in the development of hemorrhagic cystitis and bladder cancer. This study aims to determine the incidence of hemorrhagic cystitis and bladder cancer with intravenous low-dose CYC therapy used in the treatment of rheumatic diseases. A total of 211 adult patients with rheumatic disease treated with intravenous CYC were evaluated in this retrospective study conducted between January 2006 and May 2021. Patient data including cumulative CYC dose, treatment frequency, duration of treatment, side effects, such as hemorrhagic cystitis and bladder cancer were acquired from medical archives. The mean follow-up period was 48.5 (3–180) months, and the mean cumulative CYC dose was 5g (2–19g). None of the patients received mesna therapy concurrent with CYC therapy. 11 patients developed hemorrhagic cystitis (5.2%). Hemorrhagic cystitis was found to be statistically significantly associated with the number of CYC cycles (p=0.04). All patients were asymptomatic. No statistically significant difference was observed between hemorrhagic cystitis, treatment duration, and cumulative dose for CYC therapy in rheumatic diseases. Malignancy developed in 12 patients (5.7%) after CYC treatment. Bladder cancer was observed in 1 patient. According to our findings, the only risk factor for hemorrhagic cystitis in patients receiving CYC was the number of CYC cycles. Intravenous CYC regimen did not cause symptomatic hemorrhagic cystitis. Low-dose IV CYC may be safe in terms of serious urotoxic side effects when used at the appropriate dose, duration and frequency.

Keywords: Cyclophosphamide, cystitis, hematuria, rheumatic diseases, side effects

Introduction

Cyclophosphamide (CYC) is an immunosuppressive alkylating drug used to treat severe organ involvement in autoimmune inflammatory diseases, such as systemic lupus erythematosus, vasculitis, systemic sclerosis, and rheumatoid arthritis [1-3]. CYC treatment should be used with caution because of its side effects despite its effectiveness [2].

The most common side effects and complications encountered in CYC treatment are gonadal dysfunctions, teratogenicity, infections, hair loss, nausea/vomiting, bone marrow suppression, urinary bladder cancer, increased risk of malignancy, and hemorrhagic cystitis [1,3]. CYC metabolites are toxic to the urothelium, and it can cause hemorrhagic cystitis in the short term and bladder malignancy in the long term [1,2]. Hemorrhagic cystitis was characterized by hematuria, which may be accompanied by dysuria, urinary frequency, and urgency [4]. In patients receiving CYC, simultaneous oral or intravenous use of mesna, which binds to the toxic CYC metabolite acrolein, is recommended [1,5-7]. The major risk factors for bladder cancer and hemorrhagic cystitis are the duration and cumulative dose of CYC therapy [3].

CYC can be given via different routes of administration (oral or parenteral) and it can be used in different doses [3,8-11]. The risk of hemorrhagic cystitis among rheumatology patients varies according to the route of administration, wherein it is highest under continuous daily oral administration [1]. Since, the total cumulative dose is higher with oral administration [1].

Currently, there is a lack of evidence showing a relationship between hemorrhagic cystitis or bladder cancer in intravenous (i.v.) CYC therapy [1,3,8,12]. In this study, we aimed to determine the incidence of bladder toxicity due to low-dose IV CYC in rheumatic diseases.

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Materials and Methods

Participants

The study was approved by the X University Institutional Review Board and Ethics Committee (Project no: KA21/74) and supported by the Baskent University Research Fund. Informed consent was obtained from all participants. All procedures that involved human participants were performed in accordance with the ethical standards of the Institutional Research Committee and in accordance with the 1975 Helsinki Declaration and its later amendments or comparable ethical standards.

A total of 262 adult patients who were treated with IV CYC in the Rheumatology Department of X between January 2006 and May 2021 were included in this study.

The inclusion criteria were as follows: Patients diagnosed with a rheumatic disease and treated with CYC for at least three months.

Exclusion criteria were as follows: Patients younger than 18 years and those with kidney malformation and nephrolithiasis.

Data for all patients were obtained from their medical records, retrospectively. Among the 262 patients, microscopic hematuria was detected in 51 patients at the first examination due to kidney involvement. These patients were excluded from the study. The remaining 211 patients were evaluated for hematuria after CYC treatment.

The variables obtained for analysis were as follows: Diagnosis of rheumatic disease, demographic characteristics, clinical, laboratory, and radiological findings, number of CYC cycles, CYC cumulative dose, and duration of CYC treatment. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum creatinine, newly developed hematuria, and other side effects due to CYC were recorded. Morning urine samples were analyzed with dipstick and microscopy.

The patients with hemorrhagic cystitis were diagnosed during basic urinalysis screening. All patients with hematuria were evaluated with ultrasonography, urine culture, and urinalysis. Hematuria occurring in the absence of urinary tract infection, nephrolithiasis, erythrocyte casts, or decreasing renal function was defined as hemorrhagic cystitis [2]. Cystoscopic biopsy performed in one case with unexplained persistent hematuria.

Treatment Procedure

In patients with major organ involvement, intravenous CYC and corticosteroids were used for remission induction treatment. For the treatment of lupus nephritis and systemic necrotizing vasculitides, a fixed dose of 500 mg IV CYC therapy per two weeks recommended in various studies [9-11]. CYC was given intermittently depending on disease activity (every 15 days for the first month, every 2-3 weeks for the next two months, and then every 6-8 weeks). Dose reduction was performed in patients with low creatinine clearance.

Prednisolone was continued as IV 500 mg/day for 3-5 days depending on the disease activity, then 1 mg/kg/day orally. The dose was reduced to reach a dose of 10-15 mg/day within 3 months. In this study, none of the patients received mesna therapy concurrently with CYC therapy.

Statistical Analysis

Statistical analysis was performed using the statistical package SPSS software (Version 25.0, SPSS Inc., Chicago, IL, USA). For each continuous variable, normality was checked by Kolmogorov Smirnov and Shapiro-Wilk tests and by histograms. All numerical data are expressed as median values (minimum-maximum) or as proportions. The categorical variables between the groups were analyzed by using the Chi-square test or Fisher Exact. For comparisons between groups, Mann-Whitney U test was used for comparisons that were not normally distributed. $p<0.05$ was considered statistically significant in all tests.

Results

Patient Profile

The mean age of the 211 patients studied was 57 years, and 74% of them were female. The follow-up duration was 48.5 (3–180) months. Demographic, clinical and laboratory findings of the patients are shown in Table 1. The diagnoses and major organ involvement of the patients are shown in Table 2. The common diagnoses among the patients were vasculitis, rheumatoid arthritis, and systemic lupus erythematosus, respectively.

Table 1. Patients' demographic, clinical and laboratory data

Parameters	Values (n: 211)
Gender (female)*	157(74)
Age (years)**	57±13.7
Follow-up duration (months)***	48.5(3-180)
Survival*	190(90)
ESR, mm/h***	45(4–123)
C-Reactive Protein, mg/dl***	12(0-315)
Creatinine, mg/dl***	0.7(0.2-10)
Number of CYC cycles ***	10(4-38)
CYC cumulative dose (g)***	5(2-19)
CYC treatment duration(month)***	12(3-52)
Time after CYC (month)***	36(1-108)
Hematuria at follow-up	11(5.2)

ESR=erythrocyte sedimentation rate, CYC=cyclophosphamide, *n(%), **mean±SD, ***median (min - max)

The clinical indications of CYC treatment are as follows: Lung involvement (58.8%), central nervous system involvement (16.1%), kidney involvement (11.8%), lung and kidney involvement (3.8%), vascular involvement (3.8%), myositis (2.4%), hematological involvement (1.9%), and skin involvement (1.4%) (Table 2).

Hemorrhagic Cystitis and Bladder Malignancy

The number of patients who developed hemorrhagic cystitis in the follow-up was 11 (5.2%). Hemorrhagic cystitis was found to be statistically significantly associated with the number of CYC cycles ($p=0.04$). There was no relationship between hemorrhagic cystitis and CYC duration, CYC cumulative dose, age, gender, smoking, CRP, ESR, and creatinine (Table 3).

Table 2. Clinical features and diagnosis of patients receiving cyclophosphamide therapy

Main diagnosis:	Clinical Features, n	n: 211 (%)
Vasculitis*	Lung involvement, 24	
n: 48	Lung-renal involvement, 8	
26 GPA, 9 MPA	Neurological involvement, 7	48 (22.7)
8 EGPA, 2 TA	Vascular involvement, 5	
2 GCA, 1 CNS	Renal involvement, 4	
Rheumatoid arthritis	Lung involvement, 37	32 (15.2)
	Cutaneous vasculitis, 2	
Systemic lupus erythematosis	Renal involvement, 14	31 (14.7)
	Neurological involvement, 13	
	Hematological involvement, 4	
	Lung involvement, 1	
Sjögren's syndrome	Lung involvement, 20	31 (14.7)
	Neurological involvement, 7	
	Renal involvement, 4	
Systemic sclerosis	Lung involvement, 24	28 (13.3)
	Renal involvement, 2	
	Neurological involvement, 1	
	Skin involvement, 1	
Connective tissue disease	Lung involvement, 13	14 (6.6)
	Renal involvement, 1	
Behcet's disease	Neurobehcet, 6	9 (4.3)
	Vascular involvement, 3	
Polymyositis	Myositis, 5	7 (3.3)
	Lung involvement, 2	
Sarcoidosis	Lung involvement, 3	3 (1.4)

GPA=granulomatosis with polyangiitis, MPA= microscopic polyangiitis, EGPA= eosinophilic granulomatosis with polyangiitis, TA= takayasu arteritis, GCA= giant cell arteritis, CNS=central nervous system; *n (%)

Table 3. Comparison of baseline characteristics of patients with and without hematuria at follow-up

	Hematuria on follow-up (n= 11)	Without hematuria on follow-up (n=200)	p
Demographic characteristic			
Age (years)**	59.4±17.1	57.4±13.5	0.63
Gender (female)*	11(100)	146(73)	0.07
Smoking*	2(18.2)	42(21)	0.59
Clinical characteristics			
Number of CYC cycles***	16(6-28)	10(4-38)	0.04
CYC cumulative dose (g)***	8(3-14)	5(2-19)	0.05
CYC treatment duration (month)***	24(6–40)	12(3-52)	0.16
Laboratory characteristics			
CRP, mg/L***	24(2-172)	12(0-315)	0.65
ESR, mm/h***	60(34-98)	45(4-123)	0.26
Creatinine, mg/dl***	0.7(0.5-1.5)	0.7(0.2-10)	0.77

ESR=erythrocyte sedimentation rate, CRP=C-reactive protein, CYC=cyclophosphamide, *n(%),**mean ±SD,***median (min-max), p<0.05 significant

During the follow-up, cystoscopic biopsy performed in one case with unexplained persistent hematuria. And pathological evaluation revealed bladder cancer on 48 months after the treatment was completed. Malignancy detected in 12 patients (5.7%) after CYC treatment. Breast cancer was detected in 2 patients, lung cancer in 2 patients, rectum cancer in 2 patients, thyroid cancer in 2 patients, pancreatic cancer in 1 patient, prostate cancer in 1 patient, vulvar cancer in 1 patient, and bladder cancer in 1 patient. Urogenital malignancy (bladder) detected in only one patient. The mean age of the patients who developed malignancy was 66 years. The mean age of patients with malignancy was statistically significantly higher (66 vs. 57) (p<0.01).

Discussion

Less cumulative doses of CYC and less CYC induced urotoxicity were observed with IV low-dose CYC treatment, in the present study. Although the cumulative dose was similar, the rate of hemorrhagic cystitis was higher in patients who were given CYC more frequently. We conclude that frequently given CYC may cause high-rate hemorrhagic cystitis secondary to the chronic irritation on the urothelium.

Although hemorrhagic cystitis is a well-known complication of CYC, its incidence in the rheumatology literature varies [1,2]. Yılmaz et al. [2] found an incidence rate of 1.67% for hemorrhagic cystitis in patients who received CYC. Reinhold-Keller [13] et al. reported the development of hemorrhagic cystitis with CYC treatment in 12% of their patients with granulomatous with polyangiitis. The incidence rate of hemorrhagic cystitis in our study was 5.2%. Yilmaz et al. [2] showed that the cumulative CYC dose (>10g) was an independent risk factor for hemorrhagic cystitis. Monach et al. [1] found that the CYC dose rather than the CYC route of administration was the main factor for bladder toxicity. But no significant difference was found between hemorrhagic cystitis and CYC duration or cumulative dose in our study. This finding may be due to the low cumulative CYC dose we administered. The mean cumulative CYC dose used in the study of Yılmaz et al. [2] was 9g, whereas the mean cumulative CYC dose was 5g in our study. The cumulative dose is significantly lower with IV CYC compared to oral CYC regimens [1,2,14].

Low-dose pulse CYC is often preferred in rheumatic diseases because of its low side effect profile and strong efficacy [14]. In our study, we used low-dose IV CYC (500mg), a mean number of CYC cycles of 10, and a cumulative CYC dose of 5g. The CYC dose we used to be lower than that of Yılmaz et al. [2]. We did not combine CYC with mesna for uroprotection. Although the incidence rate of hemorrhagic cystitis was higher in our study than in that of Yılmaz et al., [2] none of our patients had macroscopic or symptomatic hematuria. No treatment was required other than oral hydration. Although we used 1–1.5 g/month CYC for the first three months in our treatment protocol, we did not encounter serious and symptomatic hemorrhagic cystitis that required treatment. We did not observe any relation between hemorrhagic cystitis and renal dysfunction.

In our risk factor analysis, no factors were found to be associated with hemorrhagic cystitis, except for the number of CYC cycles (p=0.04). The number of CYC cycles were higher in the hematuria group when patients with and without microscopic hematuria were compared (16 vs. 10). In our study, although the cumulative

dose was similar, the rate of hemorrhagic cystitis was higher in patients who were given more frequent CYC. This may be due to the chronic irritation of frequently given CYC, on the urothelium.

Williams et al. [15] found a statistically significant difference between CYC duration, cumulative dose, smoking and hematuria. They showed that hematuria was a risk factor for the development of bladder cancer in patients receiving CYC [15]. In our study, no relationship was found between hematuria and bladder cancer. A longer follow-up period is required to assess bladder cancer risk.

Yılmaz et al. [2] showed that concomitant mesna administration is not protective in terms of hemorrhagic cystitis in patients receiving CYC. Although mesna was not used in our study, symptomatic hemorrhagic cystitis did not develop in any patient.

In a study a twofold increase in the risk of bladder cancer was found for every 10 g increase in CYC dose [5]. In the literature, the incidence of bladder cancer after CYC treatment has been reported as 2% at 5 years and 16% at 15 years [15]. Our results showed that the total malignancy rate was 5.7%. Bladder cancer was observed in one patient 48 months after the treatment completion.

The limitations of our study are that it is a retrospective study. Urotoxicity caused by IV CYC can be better predicted by prospective comparative studies. The strength of our study was the regular and long-term follow-up.

Conclusion

In our study, less cumulative doses of CYC and less CYC induced urotoxicity were observed with IV low-dose CYC treatment. The rate of hemorrhagic cystitis was higher in patients who were given CYC more frequently, while the cumulative dose was similar. This may be due to the chronic irritation on the urothelium with frequently given CYC. Low-dose IV CYC may be safe in terms of serious urotoxic side effects when used at the appropriate dose, duration and frequency.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
The study was approved by the X University Institutional Review Board and Ethics Committee (Project no: KA21/74) and supported by the Başkent University Research Fund.

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