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ORIGINAL ARTICLE

Hemorrhagic cystitis in children treated with alkylating agent cyclophosphamide: The experience of a medical center in Taiwan

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Background/Purpose: Hemorrhagic cystitis is a common complication with chemotherapeutic alkylating agents. We investigated the possible prognostic factors of cyclophosphamide-induced hemorrhagic cystitis in children.
Methods: Medical records of children (< 18 years old) with cyclophosphamide-related hemorrhagic cystitis were collected retrospectively from January 2000 to December 2010 in a tertiary care center. We also prospectively enrolled children (< 18 years old) with cyclophosphamide treatment.
Results: The retrospective study consisted of 23 patients whose median age was 11 years. The median day of onset time was 1 day after cyclophosphamide usage. The hemato-oncological diseases included acute leukemia (39.1%), lymphoma (13%), blastoma (13%), sarcoma (13%), aplastic anemia (13%), and others (8.7%). Patients who received bone marrow transplantation (BMT) had significantly longer duration of hemorrhagic cystitis than those who did not receive BMT ($p < 0.05$). Serum uric acid, checked prior to and after the onset of hemorrhage cystitis, was significantly lower after the development of hemorrhagic cystitis ($p < 0.05$). In the prospective study, 11 children were enrolled with a median age of 5 years. The urinary nitrite/nitrate and 8-iso-prostaglandin F2α levels increased significantly after cyclophosphamide usage ($p < 0.05$).

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Conclusion: Alteration serum uric acid level and BMT could be indicators for severe hemorrhagic cystitis. The elevated levels of urinary nitrite/nitrate and 8-iso-prostaglandin F2α may indicate the essential roles played by nitric oxide syntheses and reactive oxidative stress in cyclophosphamide-induced hemorrhagic cystitis. These findings may help clinicians formulate a better strategy for treating cyclophosphamide-induced hemorrhagic cystitis.

Introduction

Cyclophosphamide is a common alkylating antineoplastic agent for chemotherapy[1,2] with the common side effect of causing hemorrhagic cystitis in children.[3] Complications of cyclophosphamide include urothelial damage with bladder edema, ulceration, neovascularization, hemorrhage, and necrosis. Incidence rates between 7% and 70% have been reported in children with hemorrhagic cystitis.[4,5] There are often marked morbidities and mortalities with severe hemorrhagic cystitis in children. Mesna (2-mercaptoethane sulfonate), high fluid intake, diuretics, and urine alkalinization are the most common treatment strategies for the prevention of hemorrhagic cystitis.[6–8] However, cyclophosphamide-induced hemorrhagic cystitis is still significantly noted even after this side effect has been clinically managed.

Although previous studies suggested the potential mechanism of hemorrhagic cystitis in children with chemotherapy, the data are limited and the prognostic factors remain to be established.[9–11] Inducible NO synthase (iNOS) was originally induced by inflammatory mediators in variable cell types,[12] and hemorrhagic cystitis has been found to induce iNOS expression in the urinary bladder of rats.[13] In addition, 8-iso-prostaglandin F2α produced by free radical-induced peroxidation of arachidonic acid are widely used as a biomarker of peroxidation and oxidative stress in adults.[14] According to previous studies, urinary 8-iso-prostaglandin $F_{2\alpha}$ levels served as the reactive oxidative stress indicator of oxidative severity in asthma, chronic obstructive pulmonary disease, interstitial lung disease, and renal injury.[15,16] Abraham and Isaac[17] found that increased malondialdehyde could serve as the oxidative stress parameter in the kidneys of rats after treatment with cyclophosphamide. However, little information is available about the severity assessment and predictor of cyclophosphamide-induced hemorrhagic cystitis. The implication of NOS and reactive oxidative species (ROS),

Table 1 Characteristic features in 23 patients with hemorrhagic cystitis.

No.	Age (y)	Sex	Daily CYC dose; administration route	Total CYC dose (mg)	Use of mesna	Uric acid (pre/post) (mg/dL)	Onset time (d)	BMT	Duration of hemorrhagic cystitis (d)	BUN/Cre (mg/dL)	Outcome
1	3	F	300 mg/m^2; IV	900	Y	4.2/3	1	−	6	14.3/0.3	
2	3	M	60 mg/kg; IV	1540	Y	N/4.5	12	−	6	12.9/0.6	
3	4	F	60 mg/kg; IV	2100	Y	4.6/3	1	+	9	14.4/0.4	
4	5	M	60 mg/kg; IV	2520	Y	6.1/2	13	+	30	40.4/0.4	Death
5	6	M	1000 mg/m^2; IV	1640	Y	3.5/N	1	−	3	4.1/0.3	
6	6	F	440 mg/m^2; IV	2920	Y	N/N	1	−	5	7.8/0.8	
7	9	F	50 mg/kg; IV	5040	Y	4.9/1.8	6	+	16	10/0.4	
8	10	F	2100 mg/m^2; IV	1650	Y	5.4/3.5	3	−	4	11.7/0.6	Late death
9	10	M	50 mg/kg; IV	8000	Y	5.2/1.9	1	+	5	6.5/0.4	Late death
10	10	M	60 mg/kg; IV	6800	Y	2.4/2.4	1	+	28	13.1/0.7	Late death
11	11	M	1000 mg/m^2; IV	9500	Y	4.2/2.3	1	+	60	9.9/0.4	
12	11	M	200 mg/m^2; IV	6360	Y	N/18.7	1	−	15	75.6/9.9	Death
13	11	M	200 mg/m^2; IV	1350	Y	7.9/N	4	−	4	7.9/0.5	
14	11	F	60 mg/kg; IV	4660	Y	4.1/2.6	12	+	62	23.6/0.6	
15	12	M	200 mg/m^2; IV	1500	Y	6/N	1	−	7	4.7/0.5	
16	12	M	60 mg/kg; IV	3600	Y	6.9/2.6	2	+	6	6.1/0.4	Late death
17	13	F	50 mg/kg; IV	3260	Y	7.9/3.9	1	+	9	18/0.6	
18	14	M	60 mg/kg; IV	5800	Y	10.2/3.3	1	+	15	17.8/0.7	
19	16	F	60 mg/kg; IV	6240	Y	4.35/2.4	1	+	15	6.3/0.6	Late death
20	16	F	1000 mg/m^2; IV	2100	Y	3.9/3.4	3	−	12	8.4/0.4	Late death
21	17	M	60 mg/kg; IV	7200	Y	4.9/2.4	10	+	31	32.4/0.9	Death
22	17	F	60 mg/kg; IV	6890	Y	4.2/1.7	1	+	19	7.1/0.5	
23	16	F	60 mg/kg; IV	6100	Y	6.3/N	1	−	4	N/N	

BMT = bone marrow transplantation; BUN/Cre = blood urea nitrogen/creatinine; CYC = cysclophosphamide; IV = intravenous; Late death = death within 1 year; N = no data.