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The Effect of Corticosteroid Eye Drops on the Prevention of Eye Disorders Caused by High-Dose Cytarabine Therapy

Tetsuo Kume[1], Kana Akiyama[1], Shigeyo Sakata[1], Takahiro Mochizuki[1], Ikue Shiki[2], Satoshi Motokawa[1,3], Michihiro Shino[1] and Takashi Ikeda[2]*

[1]Department of Pharmacy, Shizuoka Cancer Center, Japan

[2]Department of Hematology and Stem Cell Transplantation, Shizuoka Cancer Center, Japan

[3]Department of Pharmacy, Kushiro City General Hospital, Japan

Abstract

Side effects of high-dose cytarabine (HDCA) treatment include cytarabine syndrome with symptoms such as fever, muscle pain, and conjunctivitis. The use of corticosteroid eye drops to prevent eye disorders caused by HDCA has been previously reported. However, previously reported prophylactic methods include the administration of corticosteroid eye drops combined with other eye droups, we retrospectively examined the prophylactic effect of 0.1% fluorometholone eye drops (FM) as a monotherapy to prevent eye disorders caused by HDCA. The subjects were hospitalized patients who received HDCA at doses of at least 1 g/m2 between April 2011 and December 2014 at a Japanese cancer treatment center. Patients taking HDCA once a day received FM every 6 h in both eyes, starting from the first HDCA dose and continuing until 48 h after the last dose. Patients taking HDCA twice a day were administered FM every 4 h in both eyes, starting from the first HDCA dose and continuing until 48 h after the last dose. The incidence of Grade 1 and Grade 2 eye disorders was 2.8% and 2.3%, respectively, and Grade 3 eye disorders were not detected. The use of FM as a single agent appears to prevent eye disorders caused by HDCA, with the added advantage that it is a simple technique, which can be managed by the patients themselves.

Keywords: Eye disorders; Fluorometholone eye drops; High-dose cytarabine; Prophylactic effect; Simple technique

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Correspondence:
Tetsuo Kume, Department of Pharmacy, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan, Tel: +81-55-989-5222; E-mail: t.kume@scchr.jp

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Introduction

High-dose cytarabine (HDCA) is used to treat acute myeloid leukemia, acute lymphoblastic leukemia, and as a salvage treatment for malignant lymphoma [1–3]. Side effects of HDCA include cytarabine (AraC) syndrome, which manifests as fever, muscle pain, and conjunctivitis. Eye disorders resulting from AraC treatment present symptoms such as eye pain, foreign body sensation, photophobia, and conjunctivitis, and it has been reported that these symptoms develop when AraC is transported from the blood into tear fluid, inhibiting the division of corneal epithelial cells. The plasma half-life of HDCA is 2–3 h in the β-elimination phase, and approximately 3 h in tears. Even when AraC concentration in tears is approximately one tenth of the concentration in blood, it exerts a cytotoxic effect on corneal epithelial cells, leading to eye disorders [4–6].

The use of corticosteroid eye drops to prevent eye disorders caused by HDCA has been previously reported. Published prophylactic methods include the administration of corticosteroid eye drops combined with artificial tears, and using corticosteroid eye drops with sterile saline as an eye rinse [5,7,8]. However, combining prophylactic methods is more complex than using a single agent. Therefore, in this study we used a simple method to prevent eye disorders caused by HDCA, the administration of 0.1% fluorometholone eye drops (FM) as monotherapy, and examined the prophylactic effects retrospectively.

Materials and Methods

Patients and medication

The Shizuoka Cancer Center (SCC) Ethics Committee approved our study design and publication of the results. The Ethics Committee waived the requirement for informed consent because of the retrospective nature of the study. The study population comprised patients who were hospitalized and treated with HDCA at a dose of 1g/m^2 or more at the SCC between April 2011 and December 2014.Considering the incidence of side effects such as increased intraocular pressure,

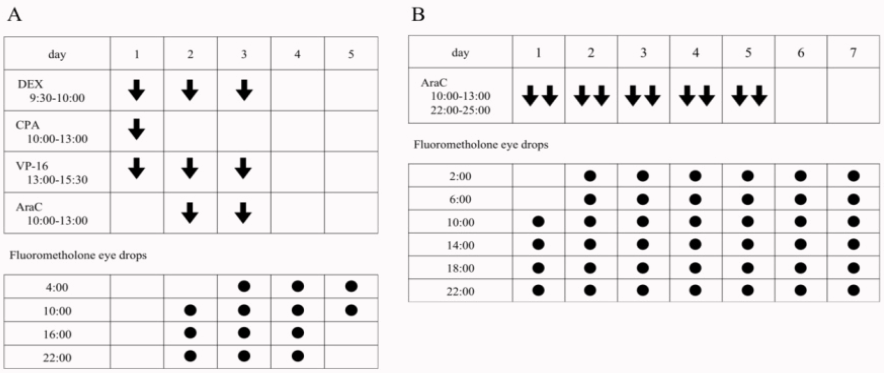

Figure 1: (A) Administration method of 0.1% fluorometholone eye drops 4 times a day. (B) Administration method of 0.1% fluorometholone eye drops 6 times a day. DEX: Dexamethasone; CPA: Cyclophosphamide; VP-16: etoposide; AraC: Cytarabine.

Table 1: Patient characteristics.

Characteristic	
Number of patients	95
Total treatment courses	213
Gender (male/female)	66/29
Age, median (range)	56.0 (18–78)
Diagnosis	
DLBCL	30
HL	5
PMBCL	5
PTCL-NOS	4
PCNSL	4
MCL	4
AML	22
Ph(−)ALL	8
Ph(+)ALL	4
Others	13
Single dose of AraC (g/m^2)	
1.00–1.50	53
1.51–2.00	138
2.01–3.00	22
TBI	4

DLBCL: Diffuse Large B-cell Lymphoma; HL: Hodgkin Lymphoma; PMBCL: Primary Mediastinal Large B-cell Lymphoma; PTCL-NOS: Peripheral T-cell Lymphoma Not Otherwise Specified; PCNSL: Primary Central Nervous System Lymphoma; MCL: Mantle Cell Lymphoma; AML: Acute Myeloid Leukemia; Ph(−) ALL: Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia; Ph(+) ALL: Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia; TBI: Total Body Irradiation.

we selected 0.1% FM administered as corticosteroid eye drops to prevent the occurrence of eye disorders caused by AraC. During the instillation period, considering the plasma half-life of AraC, patients who were administered HDCA once a day received FM every 6 h in both eyes, starting from the first HDCA dose and continuing until 48 h after the last HDCA dose. Patients who were administered HDCA twice a day received FM every 4 h in both eyes, starting from the first HDCA dose and continuing until 48 h after the last HDCA dose. The two treatment regimens are shown in (Figure 1A and 1B).

Table 2: Grades of eye disorders and AraC doses at the time of eye disorder expression.

Characteristic		p value*
Eye disorders, n (%)		
All grades	11/213 (5.2%)	
Grade 1	6/213 (2.8%)	
Grade 2	5/213 (2.3%)	
Grade 3	0	
Single AraC dose (g/m^2)		0.34
1.00–1.50	1/53 (1.9%)	
1.51–2.00	8/138 (5.8%)	
2.01–3.00	2/22 (9.1%)	
Daily AraC dose (g/m^2)		0.32
≤4.0	9/182 (4.9%)	
>4.0	2/20 (10.0%)	
Total AraC dose/cycle (g/m^2)		0.04
≤8.0	4/144 (2.8%)	
>8.0	7/58 (12.1%)	

*Fisher's exact test.
AraC: cytarabine

Assessment and grading

The items assessed included AraC dosage, presence or absence of Total Body Irradiation (TBI), and eye disorders. These data were retrieved from the medical records of the patients. To assess the eye disorders, we, along with an ophthalmologist, evaluated our departmental findings in reference to the Common Terminology Criteria for Adverse Events, version 4.0. Assessment criteria were as follows: Grade 0, none; Grade 1, eye discharge, mild symptoms of conjunctivitis, and no intervention indicated; Grade 2, symptomatic, medical intervention indicated; Grade 3, limiting self-care and activities of daily living. The assessment period lasted from the first HDCA dose until 7 days after the last HDCA dose, or until the complete resolution of any eye disorder. The highest-grade eye disorder during that period was noted. Eye disorders were assessed retrospectively based on medical records compiled by pharmacists, nurses, and physicians.

Statistical analysis

We used Fisher's exact test, and p values <0.05 were considered

Table 3: Comparisons between the present study and other reported studies.

	Prophylaxis	n	Period Start / Stop	Eye disorders
Itoh et al.[5]	0.1% BM	16	The first day / 10 days after	19%
Mori et al.[7]	0.1% BM + artificial tears	53	1 day before / 1 day after	77.3%
Mori et al.[8]	0.1% BM + sterile saline	23	1 day before / 1 day after	21.7%
Present study	0.1% FM	95	The first day / 2 days after	5.2%

BM: Betamethasone; FM: Fluorometholone.

statistically significant. All statistical analyses were performed with EZR version 3.2.2. EZR is a modified version of "R Commander" which includes statistical functions frequently used in biostatistics.

Results and Discussion

Eye disorders caused by AraC have been reported to occur when AraC is transported from the blood into tear fluid, where it subsequently inhibits the division of corneal epithelial cells [5]. In the current study, we examined the prophylactic effect of 0.1% FM as a single agent against eye disorders caused by AraC. Patient characteristics are shown in (Table 1). Of the four patients who underwent TBI, two received an AraC dose of 2g/m^2, and two received 3g/m^2. In one patient with an AraC dose of 2g/m^2, a Grade 1eye disorder was confirmed. Of the patients who were administered FM six times a day, one patient self-administered eye drops inappropriately by allowing the applicator to contact the eyelid and eyelashes, and one patient confirmed symptoms of central nervous system toxicity due to AraC. There was no difference in the incidence of eye disorders based on a single AraC dose. Therefore, we postulate that there is no relationship between a single dose of AraC and the incidence of eye disorders. On the other hand, there is a possibility that the incidence of eye disorders increases with duration of exposure to AraC.

Eye disorder grades and AraC doses at the time of eye disorder expression are shown in (Table 2). No Grade 3 eye disorders were identified in any patients who received HDCA either once a day or twice a day. Since no Grade 3 eye disorders were detected in our cohort, we believe that FM as monotherapy is an effective treatment for preventing eye disorders caused by AraC.

Previously investigated methods to prevent eye disorders include the use of corticosteroid eye drops combined with artificial tears or a sterile saline eye rinse, but it is difficult to compare those results with the findings of this study. In addition, the administration period and type of prophylactic eye drops used differ between our study and previous studies [5,7,8] (Table 3). Itoh et al. [5] administered prophylactic eye drops from the first AraC dose until 10 days after the last AraC dose, using 0.1% betamethasone as a single agent. In the current study, we administered prophylactic eye drops from the first AraC dose until 48 h after the last AraC dose, using FM as monotherapy. There was no change in the instillation schedule in most cases. Although Grade 2 or lower eye disorders were detected even with FM administration, symptoms could be controlled with treatment according to the prescribed schedule. Therefore, our use of FM as a single agent to prevent eye disorders was simpler than other methods, and was shown to have a sufficient prophylactic effect despite the presence of minor eye disorder symptoms.

Our study did have some limitations. First, the package insert for cytarabine states, "eye disorders can be prevented and reduced by corticosteroid eye drops." Therefore, it was ethically difficult to set up a comparison group that did not use corticosteroid eye drops. Second, the administration of prophylactic eye drops was essentially managed by the patients. The tip of the eye drop applicator touched the eyelashes and eyelid at the time of instillation in one case. It is possible that there were other instances of inappropriate administration of eye drops that were overlooked. Therefore, inappropriate administration of eye drops could have led to some eye disorders. Third, in this study we did not confirm the technique of eye drop administration used. It has previously been reported that instructions on eye drop administration from pharmacists resulted in the appropriate use of eye drops [5,9] Therefore, it is possible that pharmacists' instructions on the appropriate use of eye drops and confirmation of use of the correct technique by medical staff could have avoided the eye disorders observed in our study. Fourth, previous studies have reported that washing eyes with betamethasone and saline, in combination with the use of HDCA and TBI, reduced the severity of eye disorders [7]. This study did not include many patients who underwent TBI; therefore, further investigation should be undertaken with a study population including a larger number of patients who undergo TBI.

In conclusion, a prophylactic method using FM as a single agent to prevent eye disorders caused by HDCA is simpler than previously reported methods. Since we did not compare FM with other corticosteroid eye drops under the same conditions in this study, further verification is warranted.

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