We investigated the efficacy of dexamethasone plus diclofenac eye drops as prophylaxis for conjunctivitis induced by high-dose (HD) cytarabine (Ara-C). Sixty patients were randomized to receive either dexamethasone (group A, n=29) or dexamethasone plus diclofenac (group B, n=31). Conjunctivitis was experienced by 13/29 (45%) patients in group A, and 4/31 (13%) patients in group B (p<0.009). Twelve out of 13 patients in group A who developed ocular toxicity had grade 2-3 conjunctivitis whereas only one of four patients affected in group B experienced a similar grade of conjunctivitis. The incidence and severity of HD Ara-C-induced conjunctivitis are significantly reduced by combined dexamethasone/diclofenac prophylaxis.

Key words: cytosine arabinoside, conjunctivitis, prophylaxis.

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Design and Methods

Patients
Between March 2003 and October 2004, 60 consecutive patients (28 males, 32 females) with a median age of 49 years (range, 20 to 69 years) were enrolled in this study. The characteristics of the patients at the time of study entry are shown in Table 1. Criteria for exclusion were: pre-existing eye infections, conjunctivitis, or glaucoma. The study protocol was approved by the Institutional Ethical Committee and written informed consent was obtained from each patient.

Study drugs
Dexamethasone (Visumetazone®) was purchased from Visufarma S.r.l. (Rome, Italy) as a 1 mg/mL solution; diclofenac sodium 0.1% (Voltaren®) was purchased from Novartis Farma SpA (Origgio, Italy).

Study design
At the time of HD Ara-C treatment (2 g/m2 every 12 hours, intravenously, on days 1-6), patients were randomized to receive topical ophthalmic prophylaxis with either dexamethasone eye drops (two drops every 6 hours) (group A, n=29) or diclofenac eye drops (two drops every 6 hours) (group B, n=31). In both groups, ocular prophylaxis was started on day –1 (24 hours before chemotherapy administration) and continued until day 10. Group A patients developing conjunctivitis of any grade were switched within 24 hours to receive diclofenac in addition to dexamethasone.

Conjunctivitis grading
The conjunctivitis was graded according to the Common Toxicity Criteria of the National
Cancer Institute (NCI CTCAE v3.0). The criteria are: grade 1: simple eye irritation and discomfort not requiring analgesic therapy; grade 2: previous symptoms plus photophobia and inability to do normal activities. grade 3: conjunctivitis episodes requiring the use of major analgesic drugs.

**Statistical analysis**

The data were analyzed with the statistical package Prism 4.0 (GraphPad® Software, San Diego, CA, USA) run on a Macintosh G4 personal computer. Fisher’s exact test was used to determine whether there was a non-random association between two categorical variables. To test the probability of significantly different means or medians, Student’s t test for paired data (two-tail) or the Wilcoxon matched pairs test was used, as appropriate. Differences were considered statistically significant when the p value was ≤0.05.

**Results and Discussion**

Sixty consecutive patients receiving HD Ara-C (2 g/m² every 12 hours, days 1-6) as part of a high-dose sequential chemotherapy program18 were randomized to receive topical ophthalmic prophylaxis with either dexamethasone eye drops (group A, n=29) or dexamethasone plus diclofenac eye drops (group B, n=31). In both groups, ocular prophylaxis was administered from day -1 to day 10. Group A patients who developed conjunctivitis were given diclofenac in addition to dexamethasone. Table 2 summarizes the incidence, severity and duration of conjunctivitis in patients receiving dexamethasone (group A) or dexamethasone plus diclofenac (group B). The incidence of conjunctivitis was significantly higher in group A than in group B, with 13 of 29 (45%) group A patients and 4 of 31 (13%) group B patients experiencing ocular toxicity (p≤0.009). Twelve out of 13 patients in group A who developed ocular toxicity had grade 2-3 conjunctivitis with impairment of visual function and ocular pain requiring analgesic therapy. In striking contrast, only one of four affected patients in group B (25%, p≤0.008) experienced a similar grade of conjunctivitis.

Median durations of conjunctivitis in group A (4.4 days, range 2-8) and group B (3.2 days, range 2-5) patients were not statistically different (p=0.3). Since all group A patients who experienced conjunctivitis of any grade were switched to dexamethasone plus diclofenac therapy, the similar duration of conjunctivitis in the two groups essentially reflects the prompt resolution of conjunctivitis by adding the NSAID to dexamethasone.

Group A patients usually developed conjunctivitis during chemotherapy (typically, on day 3 of cytarabine treatment), whereas group B patients developed this adverse effect after chemotherapy (typically, 2 to 3 days after completing the course of cytarabine). This randomized study aimed at comparing the efficacy of two prophylactic regimens in preventing HD Ara-C-induced conjunctivitis demonstrates that the combined administration of dexamethasone plus diclofenac significantly reduces the incidence and severity of conjunctivitis as compared to dexamethasone alone. Over the last years, cytarabine has been increasingly used for the treatment of hematologic malignancies, and a spectrum of severe adverse events has been related either to the dose delivered with each infusion, or to the duration of the treatment. Conjunctivitis is a side effect reported to occur in 40 to 85% of patients receiving HD Ara-C.11 The etiology of cytarabine-induced corneal and conjunctival inflammation has been related to concentration of cytarabine in tears, which in turn seems to be dependent on cytarabine concentration in cerebrospinal fluid.16,17 Several prophylactic approaches have been investigated for their ability to prevent cytarabine-induced conjunctivitis. Higa et al.18 reported on a small series of 18 patients receiving cytarabine 3 g/m² every 12 hours for 6 days in whom ocular prophylaxis with either prednisolone eye drops or artificial tears was tested: no difference was found between the two groups. Gococo et al.11 reported that the prophylactic activities of prednisolone eye drops and of a competitive inhibitor of cytosine arabinoside, deoxycytidine, were similar. A small randomized trial conducted by Bostrom et al. on 50 patients treated with HD-cytarabine (3 g/m² every 12 hours for 6 days) documented a superior activity of deoxycytidine over artificial tears in preventing conjunctivitis.11 Currently, corticos-
teroids represent the standard prophylaxis for conjunctivitis, with the alcohol form of dexamethasone being preferred to prednisolone due to a 5- to 7-fold higher anti-inflammatory activity, and a greater capacity to penetrate the lipid rich corneal epithelium. 19

Although the most widely used method to grade conjunctivitis is qualitative, and distinguishes conjunctivitis cases as mild or severe, we found the recent NCI CTCAE v3.0 accurate and exhaustive enough. This approach provided us with a reliable and reproducible method for grading conjunctivitis without having to use flanking ophthalmic examination with a slit lamp, or rose Bengal staining.10,11

The majority of patients receiving steroid alone developed ocular toxicity earlier than patients receiving dexamethasone plus diclofenac, suggesting that diclofenac is responsible not only for reducing the incidence and severity of conjunctivitis but also for delaying the time to onset. The lower incidence and severity of overall toxicity experienced by patients in group B may be related to the combined anti-inflammatory effect, but it may also reflect the delayed onset of conjunctivitis and hence less continued exposure to cytarabine after the toxicity had occurred. Additionally, the rapid quiescence of toxicity following addition of the NSAID in patients who developed ocular toxicity while on steroid alone suggests a different effect on the inflammatory process. Indeed both drugs act on the arachidonic acid cascade, but the mechanisms of action of dexamethasone and diclofenac are partially different.14,15,20

Cyclo-oxygenase (COX) inhibitors, such as diclofenac, inhibit the cyclo-oxygenase pathway,13 whereas steroids inhibit nuclear factor κB and abrogate the arachidonic acid cascade by inhibiting phospholipase A2 through the synthesis of lipocortins.16,17

Our efficacy data should prompt future studies comparing the combination versus diclofenac as a single agent. Such studies are also warranted in view of the results of a recent randomized trial suggesting the superiority of diclofenac over dexamethasone in the field of ophthalmological surgery.20 In conclusion, combined dexamethasone/diclofenac therapy is significantly superior to dexamethasone alone for preventing cytarabine-induced conjunctivitis and should, therefore, become the standard conjunctivitis prophylaxis in patients being treated with HD Ara-C.

PM and C.C.-S contributed equally to this work. The study was performed in AMG group under the supervision of PM and CC-S; AMG, PM, CC-S, M.D.N conceived the study; AG and M.M. mostly collected data; PM, CC-S, AMG, MDN contributed to the analysis of the data; PM and CC-S wrote the manuscript with the contribution from AMG and M.M. The Authors reported no potential conflicts of interest.

This work was supported in part by grants from Ministero dell’Istruzione, dell’Università e della Ricerca (MIUR, Rome, Italy), Ministero della Salute (Rome, Italy), and Michelangelo Foundation for Advances in Cancer Research and Treatment (Milano, Italy). P.M. and C.C.-S. contributed equally to this work. Manuscript received July 9, 2005. Accepted November 21, 2005.

References


