Topical prophylaxis of conjunctivitis induced by high-dose cytosine arabinoside

Paola Matteucci
Carmelo Carlo-Stella
Massimo Di Nicola
Michele Magni
Anna Guidetti
Maddalena Marchesi
Alessandro Massimo Gianni

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 ($p \leq 0.009$). 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.

Haematologica 2006; 91:255-257

From the "Cristina Gandini" Medical Oncology Unit, Istituto Nazionale Tumori, Milano, Italy (PM, CC-S, MDN, MM, AG, MM, AMG); Chair of Medical Oncology, University of Milan, Milan, Italy (CC-S, AMG).

Correspondence:
Paola Matteucci, M.D.,
"Cristina Gandini" Medical Oncology Unit, Istituto Nazionale Tumori,
Via Venezian 1, 20133 Milan, Italy.
E-mail: paola.matteucci@istitutotumori.mi.it

High-dose (HD) cytarabine (Ara-C) is widely used either as a single agent or in combination chemotherapy for the treatment of a variety of hematological malignancies.[1-3] Although hematological toxicity is the main adverse event associated with HD Ara-C,[4,5] increasing the dose of the drug to >2 g/m^2 every 12 hours for 6 days may result in skin, gastrointestinal and cerebellar toxicity.[2,3] Conjunctivitis is observed in a significant proportion of patients treated with HD Ara-C at the dose of 2 or 3 g/m^2 every 12 hours for 6 days. Toxicity to corneal epithelium and conjunctiva is usually reversible but is often very uncomfortable, especially when associated with photophobia and ocular pain requiring analgesic treatment.[6-9] A number of prophylactic regimens have been tested to prevent HD Ara-C-induced conjunctivitis, including the use of artificial tears, steroidal compounds, or deoxycytidine.[10,11] Steroidal eye drops currently represent the standard prophylaxis of cytarabine-induced conjunctivitis which is, nevertheless, experienced by 40 to 65% of patients receiving HD Ara-C.[12] While the anti-inflammatory activity of steroids is essentially due to inhibition of nuclear factor kappa B[13] and the arachidonic acid cascade,[14] non-sterodial anti-inflammatory drugs (NSAID) mainly act by inhibiting the cyclooxygenase pathway.[15] We, therefore, hypothesized that adding a NSAID, acting with a different mechanism of action, to the standard steroidal prophylaxis might improve the therapeutic efficacy of the standard prophylaxis. To test this hypothesis, we prospectively compared the incidence, severity, and duration of conjunctivitis in a series of 60 consecutive patients who were randomized to receive either dexamethasone eye drops or an association of dexamethasone plus diclofenac eye drops.

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 Ofta®) was purchased from Novartis Farma SpA (Origgio, Italy).

Study design

At the time of HD Ara-C treatment (2 g/m^2 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 dexamethasone (two drops every 6 hours) plus diclofenac eye drops (two drops every 8 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/m^2 every 12 hours, days 1-6) as part of a high-dose sequential chemotherapy program[16] 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≥0.05). 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.[3] 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.[6-9]

Several prophylactic approaches have been investigated for their ability to prevent cytarabine-induced conjunctivitis. Higa *et al.*[17] reported on a small series of 18 patients receiving cytarabine 3 g/m^2 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.*[18] 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 30 patients treated with HD-cytarabine (3 g/m^2 every 12 hours for 6 days) documented a superior activity of deoxycytidine over artificial tears in preventing conjunctivitis.[11] Currently, corticos-

Table 1. Characteristics of the patients at the time of the study.

	Group A (n=29)	Group B (n=31)	p
Age			
Median (yrs)	50	47	n.s.
Range (yrs)	26-69	20-62	
Sex			
Males	16	12	n.s.
Females	13	19	n.s.
Histology			
DLBCL	16	17	n.s.
mantle cell lymphoma	2	2	n.s.
follicular cell lymphoma	4	4	n.s.
B-CLL/SLL	1	2	n.s.
refractory HL	2	3	n.s.
ALCL/PTCL	3	2	n.s.
Burkitt's lymphoma	1	1	n.s.
Disease status			
At diagnosis	16	22	n.s.
Refractory/relapsed	13	9	n.s.
Performance Status			
0-1	29	31	n.s.
≥2	0	0	

DLBCL: diffuse large B cell lymphoma; B-CLL/SLL: B-chronic lymphocytic leukemia/small lymphocytic lymphoma; HL: Hodgkin's lymphoma; ALCL/PTCL: anaplastic large cell lymphoma/peripheral T cell lymphoma; n.s.: not significant.

Table 2. Incidence and severity of conjunctivitis episodes.

	Patients (n)	Patients experiencing conjunctivitis	G1*	G2	G3	Median duration (days)
Group A	29	13/29 (45%)	1	8	4	4
Group B	31	4/31 (13%)	3	0	1	3

**Grading according to NCI CTCAE v3.0.*

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 exaustive 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.[11,13]

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] Diclofenac inhibits the cyclo-oxygenase pathway,[15] whereas steroids inhibit nuclear factor κ B and abrogate the arachidonic acid cascade by inhibiting phospholipase A2 through the synthesis of lipocortins.[13,14]

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 CC-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, MDN conceived the study; AG and MMar mostly collected data; PM, CC-S, AMG, MDN, AG contributed to the analysis of the data; PM and CC-S wrote the manuscript with the contribution from AMG and MMag. 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 8, 2005. Accepted November 21, 2005.

References

1. Weick JK, Kopecky KJ, Appelbaum FR, Head DR, Kingsbury LL, Balcerza S P, et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a Southwest Oncology Group study. Blood 1996; 88: 2841-51.
2. Bishop JF, Matthews JP, Young GA, Szer J, Gillett A, Joshua D, et al. A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. Blood 1996;88:754-5.
3. Herzig RH, Wolff SN, Lazarus HM, Phillips GL, Karanes C, Herzig GP. High-dose cytosine arabinoside therapy for refractory leukemia. Blood 1983; 62:361-9.
4. Rohatiner AZ, Bassan R, Raimondi R, Amess JA, Arnott S, Personen A, et al. High-dose treatment with autologous bone marrow support as consolidation of first remission in younger patients with acute myelogenous leukemia. Ann Oncol 2000;11:1007-15.
5. Mineishi S, Longo WL, Atkinson ME, Smith EP, Hamielec M, Kinsella TJ, et al. Addition of high-dose Ara-C to the BMT conditioning regimen reduces leukemia relapse without an increase in toxicity. Bone Marrow Transplant 1999;23:1217-22.
6. Hande KR, Stein RS, McDonough DA, Greco FA, Wolff SN. Effects of high-dose cytarabine. Clin Pharmacol Ther 1982;31:669-74.
7. Lazarus HM, Imperia PS, Botti RE, Mack RJ, Lass JH. An in vitro method which assesses corneal epithelial toxicity due to antineoplastic, preservative and antimicrobial agents. Lens Eye Toxic Res 1989;6:59-85.
8. Slevin ML, Piall EM, Aherne GW, Harvey VJ, Johnston A, Lister TA. Effects of dose and schedule on pharmacokinetics of high-dose cytosine arabinoside in plasma and cerebrospinal fluid. J Clin Oncol 1983;1:546-51.
9. Boos J, Bomelburg T, Gerding H, Jurgens H. Is there a relationship between cytarabine pharmacokinetics and keratitis? A case report. Int J Pharmacol Ther Toxicol 1993 31:593-6.
10. Lazarus HM, Hartnett ME, Reed MD, Murphy BF, Laas JH. Comparison of the prophylactic effects of 2-deoxycytidine and prednisolone for high-dose intravenous cytarabine-induced keratitis. Am J Ophthalmol 1987;104:476-80.
11. Bostrom B, Nelson JD, Haake R, Ramsay NKC, McGlave PB, Kersey JH. Topical deoxycytidine (dCR) to prevent ocular keratitis from high dose cytarabine (Ara-C). Proc Am Soc Clin Oncol 1988;7:282[Abstract 1095].
12. Woods WG, Ramsay NKC, Weisdorf DJ, Haake R, Vallera DA, Kim TH, et al. Bone marrow transplantation for acute lymphocytic leukemia utilizing total body irradiation followed by high doses of cytosine arabinoside: lack of superiority over cyclophosphamide containing conditioning regimens. Bone Marrow Transplant 1990; 6:9-16.
13. Chivers JE, Cambridge LM, Catley MC, Mak JC, Donnelly LE, et al. Differential effects of RU486 reveal distinct mechanisms for glucocorticoid repression of prostaglandin E release. Eur J Biochem 2004;271:4042-52.
14. Ku EC, Lee W, Kothari HV, Scholer DW. Effect of diclofenac sodium on the arachidonic acid cascade. Am J Med 1986;18-23.
15. Scholer DW, Ku EC, Boettcher I, Schweizer A. Pharmacology of diclofenac sodium. Am J Med 1986; 80:34-8.
16. Magni M, Di Nicola M, Devizzi L, Matteucci P, Lombardi F, Gandola L, et al. Successful in vivo purging of CD-34 containing peripheral blood harvests in mantle cell and indolent lymphoma: evidence for a role of both chemotherapy and rituximab infusion. Blood 2000;96:864-9.
17. Higa GM, Gokerman JP, Hunt AL, Jones MR, Horne BJ. The use of prophylactic eye drops during high-dose cytosine arabinoside therapy. Cancer 1991;68:1691-3.
18. Gococo KO, Lazarus HM, Lass JH. The use of prophylactic eye drops during high-dose cytosine arabinoside therapy. Cancer 1992;69:2866-7.
19. McGhee CN. Pharmacokinetics of ophthalmic corticosteroids. Br J Ophthalmol 1992;681-4.
20. Snir M, Axer-Siegel R, Friling R, Weinberger D. Efficacy of diclofenac versus dexamethasone for treatment after strabismus surgery. Ophthalmology 2000;107:1884-8.