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A double-blind randomized phase II study on the efficacy of topical eye treatment in the prevention of docetaxel-induced dacryostenosis

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Background: Dacryostenosis is a common side-effect of weekly docetaxel (Taxotere). We investigate the efficacy of eyedrops containing corticosteroids (CS) versus artificial tears (AT) in patients receiving weekly docetaxel in the prevention of dacryostenosis.

Patients and methods: Twenty patients receiving weekly docetaxel were evaluated. Forty eyes were double-blind randomized: AT in one eye and CS in the other eye were administered, six times daily, throughout the docetaxel administration. Patients were assessed for tearing and stenosis at weeks 3, 6, 9 and 26. The primary end point was the incidence of dacryostenosis in each group at 9 weeks.

Results: At 9 weeks, punctal or canalicular stenosis was observed in 9 of 20 (45%) of the CS eyes and 9 of 20 (45%) of the AT eyes. Dacryostenosis was mild in 37 of 40 eyes (93%) and severe in 3 of 40 eyes (8%), with equal distribution in the CS and AT group. Tearing was present in 9 of 20 (45%) of the CS eyes and 8 of 20 (40%) of the AT eyes, of which two eyes without stenosis in each group.

Conclusions: The incidence of dacryostenosis in patients receiving weekly docetaxel was not different for the AT- and the CS-treated eyes. The dacryostenosis was predominantly mild, not leading to surgical interventions.

Key words: canalicular stenosis, dacryostenosis, docetaxel, primary prevention, tearing

introduction

The antineoplastic agent docetaxel is frequently used in the management of patients with metastatic and locally advanced breast cancer and other malignancies. Docetaxel can be administered in a 3-weekly or weekly regimen. The latter provides the advantage of reduced bone marrow toxicity and related complications like febrile neutropenia, but has the disadvantage of increased dacryostenosis as secondary side-effect [1]. The incidence is reported as high as 64% in one retrospective study [2] and 30% in two later prospective studies [3, 4]. Docetaxel is secreted in the lacrimal tears [5]. It causes inflammation of the mucosa of the lacrimal outflow system resulting in fibrosis [6]. It affects predominantly the proximal lacrimal outflow system, i.e. the superior and inferior puncta and canaliculi [2, 4, 7, 8].

Importantly, tearing is not synonymous to dacryostenosis. Tearing can be the result of a reaction to dry ocular surface disease without an underlying stenosis of the lacrimal outflow system. This is called reactive tearing and is frequently present in patients undergoing chemotherapy [9]. Reactive tearing is managed with ocular lubricants like artificial tears (AT) [10]. Tearing caused by dacryostenosis is called epiphora and can only be treated surgically [4, 7]. For punctal stenosis, a punctoplasty is carried out. For subtotal stenosis of the canaliculi, temporary silicone tube stenting is advocated [7, 8]. Once total stenosis of the canaliculi is present; placement of a permanent Jones' lacrimal bypass tube is required [11].

To our knowledge, there are no studies on the primary prevention of docetaxel-induced dacryostenosis. As secondary prevention, once tearing occurs, topical corticosteroids (CS) or silicone intubation have been proposed [4]. We hypothesized that eyedrops containing CS may reduce the mucosal inflammation and hence prevent canalicular stenosis. In addition, eyedrops by itself may wash out docetaxel from the ocular surface and thereby prevent the development of dacryostenosis. We conducted a prospective, double-blind randomized, single-centre phase II trial to determine the efficacy of CS versus AT topical eye treatment starting from day 1 of cycle 1 in patients on a weekly docetaxel regimen in the prevention of dacryostenosis.

patients and methods

patients

Patients >18 years of age were included with locally advanced or metastatic cancer, for whom weekly docetaxel (Taxotere®, Sanofi-Aventis, Paris,

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France) chemotherapy was planned. Previous docetaxel administration was a reason for the exclusion. Docetaxel dose intensity had to be at least 20 mg/m^2/week during 9 weeks of treatment. Combination with other chemotherapeutic agents or with trastuzumab was allowed. All patients received standard premedication with oral methylprednisolone 32 mg b.i.d. during 2 days, from the evening before the chemotherapy administration. Patients had to be capable of administering eyedrops. Patients with glaucoma, soft contact lens wear, ocular infectious surface disease or anatomical obstruction of the lacrimal system were excluded.

methods

Before the onset of docetaxel therapy, a baseline ophthalmological examination was carried out by one ophthalmologist (BL) including the following: visual acuity, slit lamp examination, fundus examination, intraocular pressure (IOP) measurement, Schirmer's test, syringing of the lacrimal outflow system and probing of the canaliculi (Figure 1). Patients were given two blinded, identical bottles of eyedrops, marked for the right and the left eye, containing either 5 ml of AT (Lacrystat®, Meda Pharma, Brussels, Belgium) or dexamethasone sodium phosphate (CS, Maxidex®, Alcon, Fort Worth, TX). The bottles were assembled at the hospital compounding pharmacy, and the content was blinded for both the physician and the patient. Patients administered one drop six times daily, from day 1 of cycle 1, throughout the docetaxel course until 2 weeks after the last docetaxel administration. AT were used as a control, to allow patients to administer drops in both eyes. Eyedrops were applied by the patient and not by the ophthalmologist.

Patients were evaluated by the same ophthalmologist (BL) on weeks 3, 6 and 9. Evaluation at week 26 was carried out by two ophthalmologists (BL and AG). At each visit, the following exams were carried out: slit lamp examination, IOP and syringing and probing of the lacrimal system. The patency of the lacrimal system was graded: 0 for an open punctum with normal irrigation after dilation of the punctum (Figure 2A), 1 for a narrowed punctum and/or canaliculus and impaired syringing after dilation of the punctum, 2 for a narrowed punctum impossible to dilate or a narrowed canaliculus impossible to probe (Figure 2B). When stenosis was encountered, the topical therapy was continued or discontinued, with or without surgical intervention, in the best interest of the patient. The subjective complaint of tearing was graded: 0 for absent tearing, 1 for mild tearing in specific conditions (outdoors, wind, cold, etc.) that interfered with functioning but not with activities of daily living (ADL) and 2 for continuous heavy tearing interfering with ADL. Patients were excluded if ocular complications from the eyedrops were observed, in particular elevated IOP >24 mmHg. The local ethics committee approved the study and all patients gave informed consent.

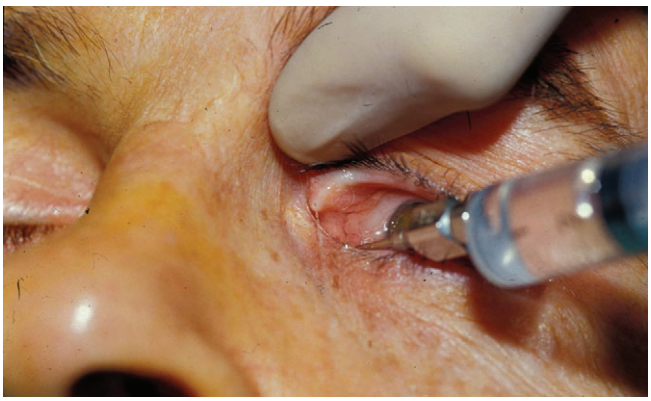

Figure 1. Examination of the lacrimal outflow system by irrigation.

statistics

statistical considerations. The purpose of the randomized phase II trial was to explore the efficacy of CS in preventing dacryostenosis during treatment with weekly docetaxel, before conducting a randomized phase III study. Eyes were randomized to be treated either with CS or with AT. In case the trial would go on as a phase III trial, the collected data of the present phase II study would be used. The primary study end point was the presence of dacryostenosis at week 9.

phase II sample size. In the literature, the incidence of dacryostenosis is reported from 30% [3, 4] to 64% [2, 12]. The reasons for this wide variety of incidence are different study designs such as retrospective versus prospective and variable inclusion criteria such as severe stenosis versus all grades of stenosis and stenosis with tearing. We assumed that for eyes receiving topical CS treatment, an incidence of 30%, including all grades of stenosis, would favor for further investigation in a randomized phase III trial.

A Simon optimum two-stage design was used [13]. If CS was ineffective, there was a 0.099 probability (alpha value) of concluding that it was effective (the target for this value was 0.10). If CS was effective, there was a 0.098 (beta value) probability of concluding that CS was not effective (the target for this value was 0.10). After testing the drug on 11 eyes of 11 patients in the first stage, the trial had to be terminated if five or fewer responded. If the trial was going on into the second stage, a total of 20 eyes of 20 patients had to be studied. If the total number of responding eyes (no dacryostenosis) was ≤10, CS would have been considered as no valuable product for the primary prevention of dacryostenosis during weekly docetaxel treatment.

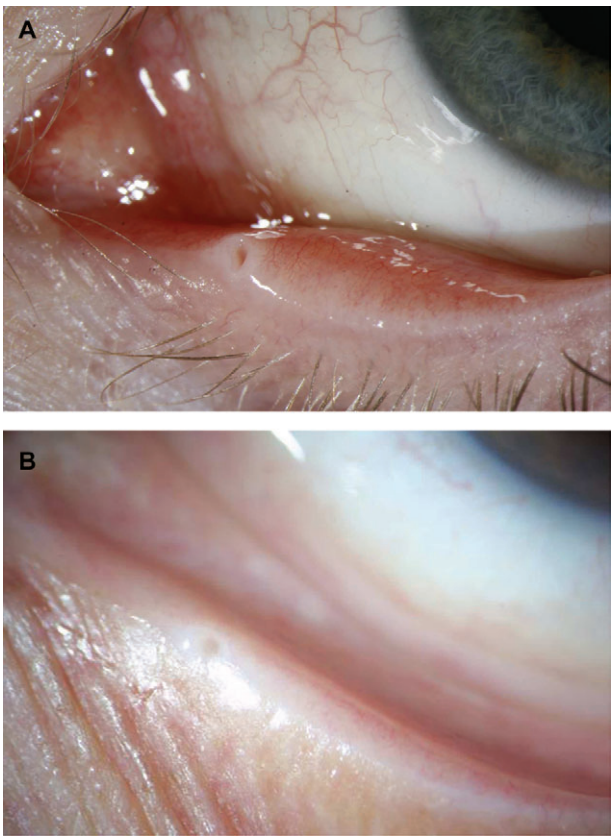

Figure 2. Photographs of two different left eyes. (**A**) Open punctum. (**B**) Grade 2 stenosis of the punctum.

analysis of the phase II trial. The patient characteristics were described with classical tests. Incidence of stenosis and tearing were reported with 95% confidence intervals for both treatment groups. No statistical hypothesis tests were carried out due to the phase II nature of the trial.

results

From July 2006 to May 2007, 29 patients were screened consecutively for the study, of whom two were not eligible due to preexisting punctal stenosis ($n = 2$) and one due to soft contact lens wear ($n = 1$). Six of the 26 included patients did not reach the primary end point: five patients had not received the predefined docetaxel dose intensity of 20 mg/m^2/week for reasons of toxicity or malignancy progression and one patient was excluded at week 3 for reasons of ocular toxicity (IOP > 24 mmHg). The phase II trial was completed because >5 of 11 of the CS group had no dacryostenosis on week 9.

The details of the 20 included patients are summarized in Table 1. Seventeen patients with metastatic breast cancer had received previous anthracyclines, 5-fluorouracil and cyclophosphamide in an adjuvant or metastatic setting. Two patients with locally advanced breast cancer and one patient with prostate cancer had not received prior chemotherapy.

Dacryostenosis developed from week 3 in one AT eye (Table 2). At 9 weeks, 9 of 20 (45%) CS eyes and 9 of 20 (45%) of the AT eyes had developed stenosis. Eight patients developed dacryostenosis bilaterally, in both the AT and CS eye. All the eyes had grade 1 stenosis, except for two CS eyes and one AT eye with grade 2 stenosis. The stenosis had an inferior monopunctal or monocanalicular affection in six of nine CS eyes and in five of nine AT eyes. Bipunctal or bicanalicular affection was observed in three of nine CS eyes and four of nine AT eyes.

At 26 weeks, grade 1 stenosis was noted in 6 of 20 (30%) of the CS eyes and 4 of 20 (20%) of the AT eyes. Of the three eyes (three patients) with previous grade 2 stenosis, one was not evaluated on week 26 (for reasons of general poor condition), one was scored grade 1 and one was scored grade 0. Nine eyes (five patients) with grade 1 stenosis at week 9 had no longer evidence of stenosis at week 26. The total of docetaxel cycles in these patients was between 8 and 14. Three eyes (two patients) had a grade 1 stenosis (monopunctal affection) at week 26 without evidence of any stenosis in the earlier controls. The total of docetaxel cycles in these patients was 7 and 15, respectively. All patients with stenosis continued the topical therapy. They were offered a surgical intervention, but all preferred to wait for reasons of limited ocular complaints.

The subjective complaint of tearing was present at week 9 in 9 of 20 of the CS eyes (of which two without stenosis) and 8 of 20 of the AT eyes (of which two without stenosis) (Table 3). Tearing and stenosis were present in 7 of 20 (35%) of the CS eyes and in 6 of 20 (30%) of the AT eyes. Tearing was noted in 9 of 11 (81%) eyes with monopunctal or monocanalicular and in 4/7 (57%) eyes with bipunctal or bicanalicular stenosis.

Two patients developed elevated IOP at week 9 in the CS eye. There was no history of pain or increased tearing in the eye. The IOP normalized 2 weeks after withdrawal of the CS drops without glaucoma drugs. In all AT eyes, the IOP remained normal during the treatment. Visual acuities did not change. No obvious changes in the lens occurred. There were no reported allergies to the eyedrops.

Table 1. Patient and treatment characteristics of all 20 patients included

	n (range)
Patients enrolled	20
Median age in years	56.5 (34–75)
Malignant disease	
Breast cancer	19
Locally advanced breast cancer	2
Metastatic breast cancer	17
Prostate cancer metastatic	1
Planned docetaxel regimen	
Docetaxel 36 mg/m^2 weekly[a]	18
Docetaxel 36 mg/m^2 2w/3[b]	2
Concomitant antitumoral therapy	
None	13
Capecitabine	3
Trastuzumab	5
Mean cumulative dose of docetaxel at 9 weeks in mg/m^2	272 (192–324)
Mean dose intensity of docetaxel at 9 weeks in mg/m^2/week	30.2 (21.3–36)
Mean total number of cycles administered	11.9 (7–17)
Mean total dose of docetaxel in mg/m^2	423 (252–612)

[a]A rest week was planned after eight cycles. Most patients received eight administrations of docetaxel at 9 weeks unless dose reductions or delays occurred.

[b]Specific regimen for locally advanced breast cancer, in combination with capecitabine (and trastuzumab in one patient).

discussion

We found an incidence of dacryostenosis of 45% in patients receiving prophylactic CS or AT eyedrops during 9 weeks of weekly docetaxel treatment. Although this phase II study does not allow formal comparison between the CS and AT treatment, it suggests that CS are not superior to AT in the prevention of dacryostenosis. It is unlikely that a phase III study would reveal a 30% superiority of CS comparing to AT.

We found mainly a mild degree of punctal and canalicular stenosis. Retrospective studies without topical eye treatment report severe stenosis, surgically treated in most of the cases [2, 8, 12]. We suggest that topical eye treatment by itself can be a determining factor in lowering the degree of stenosis. Eyedrops may wash docetaxel-containing tears out of the ocular surface and thus limit toxicity to the lacrimal system.

Tearing is a common complaint in patients receiving chemotherapy. It can be either with or without an underlying dacryostenosis, the latter being considered reactive tearing to ocular dryness. In retrospective studies on docetaxel-induced dacryostenosis, tearing is reported to vary from 19% to 70% of the patients [2, 14]. We found an incidence of tearing in 45% of the CS eyes and 40% of the AT eyes. Tearing and stenosis was present in 35% of the CS and 30% of the AT eyes, similar to

Table 2. The incidence of dacryostenosis at different week intervals

Treated eyes	Baseline	Week 3	Week 6[a]	Week 9	Week 26[b]
AT	0/20	1/20	3/18	9/20	4/16
95% CI	0% to 16.8%	0.1% to 24.9%	3.6% to 41.4%	23.0% to 68.5%	7.3% to 52.4%
CS	0/20	0/20	3/18	9/20	6/16
95% CI	0% to 16.8%	0% to 16.8%	3.6% to 41.4%	23.0% to 68.5%	15.2% to 64.6%

[a]Week 6: two patients not assessed (refusal).
[b]Week 26: four patients not assessed (three too ill and one refusal).
AT, artificial tears; CI, confidence interval; CS, corticosteroids.

Table 3. The incidence of tearing

Treatment	Baseline	Week 3	Week 6[a]	Week 9	Week 26[b]
AT	0/20	1/20	2/18	8/20	8/16
95% CI	0% to 16.8%	0% to 16.8%	1.4% to 34.7%	19.1% to 63.9%	24.7% to 75.3%
CS	0/20	1/20	3/18	9/20	8/16
95% CI	0% to 16.8%	0% to 16.8%	3.6% to 41.4%	19.1% to 63.9%	24.7% to 75.3%

[a]Week 6: two patients not assessed.
[b]Week 26: four patients not assessed.
AT, artificial tears; CI, confidence interval; CS, corticosteroids.

a previous report [3]. We found more tearing in the patients who had monopunctal or monocanalicular affection than bipunctal or bicanalicular stenosis. The lack of correlation between symptoms and grade of stenosis can be entirely explained by the factor of reactive tearing.

The proximal lacrimal system was found to be affected, which is in agreement to previous studies [1, 7]. This indicates that docetaxel-containing tears cause fibrosis at the entrance of the lacrimal apparatus. The observation of a proximal stenosis can be seen as a natural defense mechanism of the lacrimal system to prevent further distal damage. A surgical punctoplasty during the course of docetaxel treatment might therefore be considered harmful since it allows docetaxel tears to reach the canaliculi and induce more extensive, distal stenosis that is less easily operable. We therefore recommend to carry out a punctoplasty only after completion of the docetaxel treatment or in combination with silastic intubation.

We found a stenosis in both the AT- and CS-treated eye in eight similar patients, indicating a well-known individual predisposition for developing dacryostenosis.

The inconsistent data of new and disappeared stenosis at the secondary end point at 26 weeks can be explained by the interobserver difference, the last observer being less experienced with grading lacrimal systems. For ophthalmologists familiar with the lacrimal system, intraobserver reproducibility will be high. On the other hand, a mild stenosis can theoretically spontaneously reopen. The appearance of new stenosis after 26 weeks cannot be explained by a long-lasting effect of docetaxel after stopping the eye therapy since the half-life of docetaxel is ~12 h.

Oral methylprednisolone (32 mg b.i.d.) was administered the day before and the day of docetaxel therapy. There are no data on the concentration of oral methylprednisolone in tears. Chronic and daily therapy with oral methylprednisolone has known ocular side-effects due to high and constant therapeutic levels, though intermittent administration as in this study is less likely to be a factor in the prevention of dacryostenosis since the half-life of oral methylprednisolone is only 12–36 h.

The double-blinding in the present study reduced compliance-related errors since patients were not tempted to treat a control eye that would show symptoms of tearing.

In conclusion, the use of prophylactic CS eyedrops cannot prevent dacryostenosis in a weekly docetaxel administration. However, while previous studies report a high incidence of severe stenosis requiring lacrimal surgery, we generally found mild stenosis in both CS and AT groups, indicating that topical eye therapy by itself might reduce severity. AT have a nonexistent ocular toxicity compared with CS. We therefore recommend AT as a safe, prophylactic ocular treatment throughout the entire docetaxel course that will also help to control reactive tearing. Only a placebo-controlled study can give a definite answer whether prophylactic AT compared with no treatment can clinically relevantly reduce the severity of stenosis, but such a study will be much more prone to bias than the present study.

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