Evaluation and Management of Chemotherapy-Induced Epiphora, Punctal and Canalicular Stenosis, and Nasolacrimal Duct Obstruction

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Purpose: To describe the frequency, mechanisms, and treatment of epiphora caused by chemotherapeutic agents.

Methods: Review of relevant articles published in PubMed.

Results: The chemotherapeutic drugs best documented to cause epiphora are 5-fluorouracil and docetaxel; with both of these drugs, the main mechanism underlying epiphora is canalicular stenosis. Drugs less commonly reported to cause epiphora include S-1, capecitabine, imatinib, topical mitomycin C, and radioactive iodine for treatment of papillary thyroid carcinoma. While all the above-mentioned drugs can be associated with epiphora, some drugs and administration schedules cause only punctal and canalicular inflammation, whereas others cause significant canalicular stenosis. For example, weekly administration of docetaxel is far more likely to cause canalicular stenosis than every-3-weeks administration. The literature suggests that, in patients who receive weekly docetaxel, silicone stenting at the first sign of recurrent or progressive canalicular stenosis can prevent severe irreversible canalicular stenosis and avoid the need for a conjunctivodacryocystorhinostomy. S-1 and radioactive iodine have been reported to cause nasolacrimal duct obstruction. Early recognition of punctal and canalicular stenosis or nasolacrimal duct blockage and early intervention with topical steroids and canalicular stenting in patients at risk for permanent canalicular scarring are important to avoid the need for more invasive and complicated procedures.

Conclusion: A variety of chemotherapeutic agents have been reported to cause epiphora, and some of these drugs have also been documented to cause obstructions of the lacrimal drainage system. Early recognition and management of epiphora is important and leads to better outcomes.

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The lacrimal drainage system, which is covered by a highly proliferative epithelium, is susceptible to the toxic effects of chemotherapeutic drugs. Such drugs may adversely affect the lacrimal drainage system through drug secretion in tears, by producing local inflammation or through other mechanisms less well understood. Excessive tearing, or epiphora, has been reported as an adverse effect of many chemotherapeutic drugs.[1–29] Haidak et al.[2] first reported chemotherapy-induced epiphora in 1978 in a case series of 6 patients receiving chronic 5-fluorouracil (5-FU) who had epiphora and were found to have canalicular stenosis. Since that report, several other chemotherapeutic agents have been reported to cause epiphora and obstruction of the lacrimal drainage system.[1–29]

In this review, for each of the systemic and topical chemotherapeutic agents most commonly reported to cause epiphora, the authors discuss the frequency, mechanisms, and recommendations for management of epiphora.

Early diagnosis and management of epiphora and underlying punctal or canalicular stenosis and nasolacrimal duct obstruction are important for improving cancer patients' quality of life. A delay in diagnosis may lead to permanent scarring and obstruction of the canaliculi or nasolacrimal duct and the need for more invasive and extensive surgical interventions that could otherwise have been avoided.

METHODS

On November 24, 2015, the authors carried out a PubMed search of all articles on epiphora in cancer patients using the following key words in various combinations: epiphora, tearing, punctal stenosis, canalicular stenosis, nasolacrimal duct obstruction, chemotherapy, 5-FU, docetaxel, S-1, capecitabine, mitomycin c, imatinib, and radioactive iodine. Abstracts were reviewed, and if an abstract was deemed relevant and appropriate, the corresponding article was included for review.

RESULTS

5-Fluorouracil. 5-FU is a pyrimidine analog and a potent inhibitor of thymidylate synthase that is used as a single agent or in combination with other drugs in the treatment of carcinomas of the gastrointestinal tract, breast, ovaries, and skin.[8–12] Systemic 5-FU has been reported to cause ophthalmologic adverse effects, most commonly lacrimal outflow obstruction but also ocular surface irritation, keratitis, and conjunctivitis.[8] In a series of 52 adults under treatment with 5-FU for at least 3 months, excessive tearing was the most common adverse effect, reported in 14 patients (27%), and frank punctal or canalicular stenosis was reported in 3 patients (6%).[8] Other reports also indicate that the primary site of stenosis or obstruction due to 5-FU is at the puncta or canaliculi as opposed to more distal in the lacrimal drainage system.[11,30] Histologic studies have demonstrated fibrosis at the canaliculi,[2,31] the lacrimal sac,[2] and the puncta,[31] confirming the clinical findings.

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In a prospective study of patients with gastrointestinal carcinoma receiving intravenous 5-FU, epiphora developed in 10 of 20 patients (50%) receiving weekly palliative 5-FU.[30] Three of these 10 patients had frank canalicular fibrosis, and these 3 patients had received 5-FU for significantly longer and had received significantly higher doses of 5-FU than the other 7 patients. Of the 7 patients with excessive tearing without frank canalicular fibrosis, 4 patients discontinued 5-FU, and the excessive tearing in these patients resolved within 2 to 4 weeks. The association between canalicular stenosis and increasing duration and dose of treatment with 5-FU underscores the need for early evaluation and intervention at the onset of symptoms. Other reports have described similar resolution of epiphora upon completion of 5-FU therapy.[10]

The reversibility of epiphora in some patients suggests a second mechanism contributing to epiphora in addition to anatomic obstruction. There is likely a component of hypersecretion or reflex tearing in response to ocular surface irritation from secretion of 5-FU in the tear film. In fact, studies in patients treated with 5-FU have shown 5-FU in tears of patients with epiphora but not in tears of patients without ocular symptoms.[9] Another possible explanation for spontaneous resolution of epiphora in some patients treated with 5-FU is that such patients may have inflammation of the puncta and canaliculi without the end-stage fibrosis that can ensue with prolonged or more frequent administration of the drug.

The interventions that can be used to improve epiphora secondary to 5-FU range from irrigation and probing followed by administration of topical steroids to conjunctivodacryocystorhinostomy (C-DCR). In one series, in 4 of 15 patients (27%) with canalicular stenosis secondary to systemic 5-FU therapy, stenosis was so severe that C-DCR was required.[32]

Docetaxel. Docetaxel (Taxotere), a taxane, is used in the treatment of a variety of malignancies, including breast cancer, metastatic non–small-cell lung cancer, prostate cancer, gastric cancer, and head and neck cancer. Docetaxel is used both as a single agent and in combination with other drugs and is used for both palliative and adjuvant treatment. Epiphora associated with the use of docetaxel has been well described.[14–23,33]

Stenosis, primarily canalicular stenosis, was first described as a mechanism underlying docetaxel-related epiphora in 2001, in a series of 3 patients with metastatic breast cancer who presented with epiphora during weekly docetaxel therapy.[14] In a later report on a different series of 3 patients who developed epiphora during docetaxel therapy, histologic studies of biopsy specimens of lacrimal sac and nasal mucosa obtained at the time of either silicone intubation of the nasolacrimal system or dacryocystorhinostomy revealed chronic fibrosis of the mucosal stroma.[18] These histologic findings were similar to those previously described in patients receiving 5-FU. Also similar to findings with 5-FU, docetaxel has been demonstrated to be secreted in tears of patients receiving intravenous docetaxel.[16]

Both retrospective and prospective studies have shown that the schedule of administration of docetaxel significantly affects the incidence and severity of canalicular stenosis. Unfortunately, these relationships are not appreciated by many oncologists or ophthalmologists. The first report on the significant difference in frequency and severity of canalicular blockage with the 2 different schedules of administration of docetaxel was a retrospective study that found that canalicular stenosis was much more common with weekly than with every-3-weeks intravenous docetaxel in patients with metastatic breast cancer with a mean duration of treatment of 19 weeks.[22] In this study, of the 18 patients receiving weekly therapy, 14 (78%) had epiphora, and 9 (50%) had significant stenosis that necessitated either silicone intubation or C-DCR. In contrast, of the 18 patients receiving every-3-weeks therapy, only 2 (11%) reported epiphora, and none had canalicular stenosis.

This link between docetaxel dosing schedule and the risk of epiphora was further validated in the largest retrospective study on the topic, which included 148 patients treated with docetaxel at various dosing schedules: weekly in 71 patients, every 2 weeks in 5 patients, and every 3 weeks in 72 patients.[19] Most of the patients had metastatic carcinoma, but 2 patients were receiving docetaxel as neoadjuvant therapy for breast carcinoma. Of the 71 patients receiving weekly docetaxel, 30 underwent surgery to correct epiphora: 23 patients (39 eyes) had temporary silicone intubation of the canaliculi, 9 patients (13 eyes) had DCR, and 4 patients (7 eyes) had C-DCR. Of note, the oculoplastics service recommended surgical intervention in an additional 21 patients receiving weekly therapy (C-DCR in 10 patients and silicone intubation or DCR in 11 patients), but these patients chose to forego treatment. Of the patients receiving every-2-weeks or every-3-weeks treatment, only 3 required a surgical intervention to correct epiphora, and none had stenosis severe enough to warrant C-DCR.

The same authors then conducted a randomized trial of weekly versus every-3-weeks docetaxel in patients with metastatic breast cancer and reported the incidence of canalicular stenosis in each arm.[17] Patients underwent an evaluation by an oculoplastic surgeon that included probing and irrigation of the nasolacrimal system before initiation of docetaxel therapy and every 4 to 6 weeks after initiation of therapy. The authors found that 64% (18 of 28) of the patients receiving weekly docetaxel developed epiphora, in contrast to only 39% (11 of 28) of the patients receiving docetaxel every 3 weeks. Furthermore, one-third of the patients receiving weekly docetaxel had moderate to severe canalicular blockage as an anatomic finding on probing and irrigation, whereas patients receiving docetaxel every 3 weeks had epiphora but no evidence of canalicular blockage. All patients who developed epiphora were treated with topical tobramycin and dexamethasone for at least 6 weeks. Interestingly, 9 patients in each group had resolution of epiphora with this topical therapy alone. Surgical intervention was required to treat epiphora in the rest of the patients on weekly docetaxel.

A double-blind randomized prospective study of topical corticosteroid treatment to prevent stenosis due to docetaxel did not show corticosteroids to be effective.[34] In this study, 20 patients receiving weekly docetaxel treatment had 1 eye treated with dexamethasone and the other treated with artificial tears, each at a frequency of 1 drop 6 times per day for the duration of docetaxel administration. The authors reported no significant difference in the incidence of dacryostenosis at 9 weeks, found to be 45% in each cohort.

Among patients with epiphora who are receiving docetaxel every 3 weeks or who will be exposed to docetaxel for less than 3 to 4 months (e.g., those receiving docetaxel for neoadjuvant therapy), for epiphora due to mild, early canalicular or nasolacrimal duct obstruction, every-few-weeks probing and irrigation and judicious use of topical steroid drops on a tapering dose would be appropriate treatment. The literature suggests that this approach relieves epiphora in the majority of patients and prevents permanent blockage of the canaliculi and nasolacrimal duct in the overwhelming majority of patients.[23] However, among patients with epiphora who are receiving weekly docetaxel or have metastatic disease likely to be treated with docetaxel for a long period, the risk of canalicular stenosis is much higher (about 30% in patients receiving weekly docetaxel), and early bilateral silicone intubation should be strongly considered as soon as patients demonstrate signs of recurrent or progressive punctal or canalicular blockage on probing and irrigation (e.g., pain, bleeding, or a "soft stop" on probing).[17,20–23] Bicanalicular silicone intubation may prevent permanent canalicular blockage and the need for more invasive surgery such as DCR or C-DCR. The silicone tubes should be left in place for at least 2 to 3 months after cessation of docetaxel.[23]

S-1. S-1 is an oral drug composed of 3 molecules: tegafur, which is a prodrug of 5-FU, gimeracil, and oteracil, 2 other modulators of 5-FU metabolism. S-1 is widely used in Japan, primarily for treatment of gastric cancer. It is not currently approved for use in the United States. Esmaeli et al.[4] were the first to report S-1-related epiphora, in a 2005 article on 3 patients who developed epiphora after receiving S-1 plus cisplatin as a part of an ongoing clinical trial. The patients were treated

in 28-day cycles, with S-1 administered orally on days 1 to 21 and cisplatin delivered intravenously on day 1 of each cycle. These patients were receiving S-1 as monotherapy for 6 months as a part of an ongoing clinical trial. One patient's symptoms were reversed with topical therapy with prednisolone acetate 1% and tobramycin. Another patient had complete canalicular stenosis but refused surgical intervention. The third patient underwent successful C-DCR.

Since this first report, larger studies, primarily out of Japan, have further characterized the association between epiphora and S-1. A retrospective study of 55 patients treated with S-1 for at least 1 month showed that 6 of 55 patients (11%) had stenosis of the lacrimal drainage pathway at the punctum, canaliculus, or distal nasolacrimal duct.[5] The mean time to onset of epiphora after the initiation of S-1 has been reported to be 4.4 months (range, 2–8 months; standard deviation, 2.2 months).[6]

In a prospective study of 179 patients with gastric cancer receiving adjuvant S-1, Kim et al.[7] reported that 31 of 170 patients (18%) developed epiphora. Twenty-five of these patients underwent ophthalmologic evaluation, and 22 of 25 patients (88%) were diagnosed with lacrimal duct obstruction with a median time to onset of 2.9 months after initiation of S-1. Obstruction at the level of the nasolacrimal duct was the most common form of obstruction, found in 86% of the patients; punctal stenosis and canalicular obstruction were less common, found in 23% and 14% of patients, respectively.[7]

Radioactive Iodine. Radioactive iodine (^{131}I) for the treatment of thyroid carcinoma has been estimated to cause nasolacrimal duct obstruction in approximately 2% to 18% of patients..[27–29,35] The risk of obstruction increases with the dose,[27–29] and obstruction is more likely to occur with cumulative ^{131}I doses of 150 mCi or higher.[28,29,36] In patients with papillary thyroid carcinoma treated with ^{131}I, dosages of ≥150 mCi have been demonstrated on scintigraphy and single photo emission computed tomography to have higher uptake into nasal tissues compared with dosages of 100 mCi, which may explain the increased risk of toxicity to nasal tissues and to the nasolacrimal duct with increased dose.[36] A recently published review on the topic outlines the cases of nasolacrimal duct obstruction secondary to ^{131}I reported in the literature and found that females and those greater than 45 years of age are more likely to experience nasolacrimal duct obstruction from ^{131}I therapy.[35] The authors therefore recommend pretreatment screening in patients complaining of epiphora and all "high-risk" patients, defined as females, those greater than 45 years of age, and patient who will receive an ^{131}I dose of greater than 150 mCi.

Capecitabine. Capecitabine is a fluorinated pyrimidine antineoplastic agent and, like S-1, is a prodrug of 5-FU. The authors found one report in the literature of nasolacrimal duct obstruction in a patient receiving capecitabine: a 71-year-old woman in Japan who was treated with trastuzumab plus capecitabine.[13] The more commonly reported ocular adverse effect of capecitabine is ocular surface irritation, reported in 10% of patients.[37] The authors have observed that capecitabine is associated with the symptom of epiphora but the authors have never seen a patient with nasolacrimal duct obstruction or canalicular stenosis due to capecitabine treatment (personal observation by senior author BE).

Imatinib. Imatinib is a selective inhibitor of tyrosine kinases, including Bcr-Abl, c-kit, Arg, and platelet-derived growth factor receptor-related protein kinases. Imatinib is approved by the United States Food and Drug Administration for the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumor. Epiphora is the second most commonly reported ocular adverse effect of imatinib, following periorbital edema, and is reported in up to 20% of patients.[24,38,39] The mechanisms underlying imatinib-induced epiphora include conjunctival chemosis resulting in ocular surface irritation and overproduction of tears, lacrimal pump dysfunction due to periorbital edema, mechanical blockage of the puncta due to conjunctivochalasis, and secretion of the medication in the tear film.[24,38,39] Steroids and diuretics have been used in these situations. In a report by Esmaeli et al.,[24] all the patients who presented with epiphora during imatinib treatment also had periorbital edema, and none of these patients had nasolacrimal duct obstruction on probing and irrigation of the nasolacrimal duct.

Mitomycin C. Mitomycin C is an antimetabolite derived from *Streptomyces caespitosus*. This drug is used topically for the treatment of ocular surface squamous neoplasia. Punctal stenosis associated with the use of topical mitomycin C was first reported by Selva and colleagues in 2003[26] and is hypothesized to be a result of mitomycin C's proinflammatory effects that cause fibrosis.[25] Estimates of the incidence of epiphora and punctal stenosis with the use of topical mitomycin C 0.04% applied 4 times a day for one to three 7-day cycles range from 10% to 43%.[40] In a study of patients who received topical MMC 0.04% applied 4 times a daily for 2 weeks, 9 of 14 (64%) reported epiphora at 1 month after completion of treatment, found to be due to either punctual or canalicular stenosis.[25] Interestingly, mitomycin C has been reported to prevent fibrosis of the lacrimal drainage system through antiproliferative effects on DNA and fibroblast synthesis.[40]

General Recommendations for Patient Evaluation and Care. Evaluation of cancer patients with epiphora and suspected stenosis or obstruction of the lacrimal drainage system requires a careful history and evaluation. The history should include symptoms and signs of epiphora, ongoing medical problems, cancer history, medications received (including previous chemotherapy) and frequency of administration, radiation therapy, and surgery in the orbitofacial area. Evaluation should include slit lamp biomicroscopy with particular attention to the appearance and position of the puncta and the position of the lower eyelid. A Schirmer's test can provide additional information and can aid in recognition of dry eye syndrome, which may contribute to tearing. Probing and irrigation is critical to evaluate the anatomic integrity of the lacrimal drainage system.

The authors recommend that all patients treated with chemotherapeutic drugs known to cause epiphora be closely monitored by an ophthalmic plastic surgeon. Prompt referral after the onset of epiphora may obviate surgical intervention. Ophthalmic plastic surgeons should become familiar with the chemotherapy drugs that can cause epiphora and the schedules of administration associated with mild inflammation versus permanent scarring of the canaliculi to inform selection of patients for a conservative approach versus surgical intervention.

In mild cases of canalicular stenosis, probing and irrigation followed by a short course of topical steroids may be sufficient to relieve epiphora and prevent permanent blockage of the canaliculi. However, in patients receiving frequent doses of a drug (e.g., weekly docetaxel), immediate consideration of canalicular stenting at the first symptom of recurrent or progressive epiphora may be appropriate.

CONCLUSION

In conclusion, given the widespread use of many chemotherapeutic agents that can cause epiphora, it is crucial that ophthalmic plastic surgeons and oncologists be aware of stenosis or obstruction of the lacrimal drainage system as a possible adverse effect of these drugs. Timely diagnosis can prevent complete closure of the puncta or canaliculi. Referral to an ophthalmic plastic surgeon at the onset of symptoms is recommended so the appropriate intervention may be performed.

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