SYMPTOM MANAGEMENT OVERVIEW
Section Editor: Joseph Bubalo, PharmD, BCPS, BCOP

SUBMIT YOUR
SYMPTOM MANAGEMENT UPDATE

Readers are invited to submit brief updates with practice insights on the care of a specific symptom or a cluster of symptoms associated with a condition that is often seen in patients with cancer. The updates will be presented in the form of a “How I Treat” type of article.

The goal of this section is to present a quick background to enhance providers’ understanding of the symptoms associated with a specific condition and their characteristic presentation(s) and etiology. The emphasis should be on a concise description of available treatments and current course of therapy.

WHAT IS SYMPTOM MANAGEMENT OVERVIEW?

Each review should provide a brief description of the symptom(s) associated with a common condition in oncology and its evidence-based management.

ARTICLE FORMAT

- Length of article: 800-1200 words
- Tables: 1-3
- Describe the symptom(s)
- Etiology
- Treatment options: dose(s), frequency, titration parameters
- Course of therapy: time to effect/symptom resolution, expected effects, special or target populations for specific therapies, side effects and their management, as appropriate
- References: minimum 5; maximum 15

HOW TO SUBMIT
Submit a Word file of your article at www.JHOPonline.com
Prevention and Treatment of Cytarabine-Induced Keratoconjunctivitis

By Joseph Bubalo, PharmD, BCPS, BCOP
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SYMPTOM OVERVIEW

Corneal toxicity with high-dose cytarabine is a well-established risk of therapy. Routine prophylaxis with eye drops, usually topical corticosteroid drops, is an established part of high-dose cytarabine treatment protocols. Without topical corticosteroid prophylaxis, incidences of keratoconjunctivitis have been reported in 85% to 100% of cases; the occurrence of clinically significant symptoms with the use of prophylaxis is reported in 8% to 16% of cases.

ETIOLOGY

Cytarabine has a known ability to penetrate body fluids, including crossing the blood–brain barrier, and can be found in the aqueous humor and in tears. Corneal toxicity appears to be related to the concentration of cytarabine in tears, and the duration of exposure. Risk factors vary with high-dose cytarabine (Table 1), and duration of dosing is most strongly associated with the toxicity; few cases have been seen with intermittent or continuously administered intravenous, low-dose cytarabine (eg, <200 mg/m^2/day). Conjunctivitis has occurred as early as 3 days into therapy, and several days after therapy, with days 6 to 8 posttherapy the most commonly reported time of occurrence.

Findings at eye examinations have been described as bilateral corneal epithelial microcysts—possibly more densely distributed in the center of the cornea than in the midperiphery, conjunctival hyperemia, and fine corneal opacities. There is often severe blepharospasm and moderate conjunctival inflammation—however, the anterior chambers of the eyes are usually free of inflammation, and intraocular pressure is normal.

The mechanism of microcyst formation is currently unknown. Corneal epithelial stem cells have a long cycle time and are unlikely to be cytarabine-susceptible; however, they bring about more differentiated transient amplifying cells in the basal layer, which divide more frequently and may therefore be vulnerable to cytarabine toxicity. Common ocular symptoms include blurred vision, severe discomfort or burning pain, photophobia, decreased visual acuity, tearing, and foreign body sensation.

TREATMENT OPTIONS

Prophylaxis is generally not recommended at doses <1000 mg/m^2. Suggested prophylaxis is corticosteroid eye drops; however, other agents and combinations have been used successfully. These include a variety of preparations, including tear replacement solutions and topical, nonsteroidal anti-inflammatory drops. Every 4- or 6-hour administration on a strict schedule appears to provide the most benefit, and drops should be continued at least 48 hours after the last cytarabine dose. The mechanism of conjunctivitis prevention is unclear, but
may rely on a decreased replication rate induced by corticosteroids impacting DNA replication in corneal cells. An additional mechanism of action may be a diluting effect on the cytarabine concentration; 1 trial showed benefits achieved from frequent use of artificial tears. It is unclear whether components of eye solutions, especially preservatives, can exacerbate the conjunctivitis. Given the limited studies on this toxicity, preservative-free products would be preferred when available.

When conjunctivitis occurs there is no standard therapy, and treatment is often left to the local ophthalmologists, who generally apply additional corticosteroid eye drops, with other agents added in as needed. See Table 2 for a list of prophylaxes and Table 3 for treatments for cytarabine-induced conjunctivitis. Dexamethasone eye drops are the most common agent used to treat conjunctivitis, and there may be additional benefits derived by adding a topical nonsteroidal anti-inflammatory drug (NSAID). Dexamethasone has greater anti-inflammatory activity, and may have better corneal penetration than prednisolone. Pain, irritation, and other symptoms generally respond within days, with visual acuity returning to baseline by 2 weeks, and corneal opacities resolved by 4 weeks. Additional symptom benefits may be obtained through the application of cold compresses to the eye, and by keeping lights at a low level.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Prophylaxes for Cytarabine-Induced Conjunctivitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Dose</td>
</tr>
<tr>
<td>Betamethasone sodium phosphate 0.1% with natural tears or 0.1% sodium hyaluronate</td>
<td>1 drop of each every 6 hours</td>
</tr>
<tr>
<td>Betamethasone sodium phosphate 0.1% with sterile saline eye rinse</td>
<td>1 drop every 6 hours; rinse each eye with 3-4 mL of sterile saline in a commercial eye rinse cup</td>
</tr>
<tr>
<td>Dexamethasone 0.1%</td>
<td>2 drops in each eye every 6 hours</td>
</tr>
<tr>
<td>Dexamethasone 0.1% with diclofenac sodium 0.1%</td>
<td>2 drops of dexamethasone in each eye every 6 hours, and 2 drops of diclofenac in each eye every 8 hours</td>
</tr>
<tr>
<td>Artificial tears</td>
<td>2 drops in each eye every 4 hours</td>
</tr>
<tr>
<td>Natural tears</td>
<td>2 drops in each eye every 8 hours</td>
</tr>
<tr>
<td>Prednisolone phosphate 1%</td>
<td>Doses ranging from 2 drops in each eye every 8 hours to 2 drops in each eye every 4 hours</td>
</tr>
</tbody>
</table>

HSCT indicates hematopoietic stem-cell transplantation; TBI, total body irradiation.
Although it has been well-documented for >30 years, cytarabine-induced keratoconjunctivitis continues to be a poorly studied and problematic adverse effect of cytarabine use. Even though evidence has been reported that deoxycytidine, a competitive inhibitor of cytarabine, may be an effective antidote, a commercially available product for patient use is still not available. Unless a deoxycytidine product is developed and proven successful, the information currently available would support the addition of an NSAID eye drop to corticosteroids for high-risk or symptomatic patients. Additional research is clearly warranted in this area. 

References

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Treatments for Cytarabine-Induced Conjunctivitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Dose</td>
</tr>
<tr>
<td>Dexamethasone 0.1%&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>1-2 drops every 2 hours</td>
</tr>
<tr>
<td>Diclofenac sodium 0.1%&lt;sup&gt;8&lt;/sup&gt;</td>
<td>2 drops in each eye every 8 hours</td>
</tr>
</tbody>
</table>
7:00 am – 8:00 am  Meet the Experts Breakfast
8:00 am – 8:15 am  Introduction and Opening Remarks
          Barbara L. McAneny, MD, American Medical Association
          Sanjiv S. Agarwala, MD, Temple University School of Medicine
8:15 am – 9:15 am  Session 1 - Win-Win-Win Approaches to Oncology Care:
          How Providers, Patients, and Payers Can All Benefit from
          Improving the Way We Pay for Cancer Treatment
          Harold Miller, Center for Healthcare Quality and Payment Reform
9:15 am – 10:00 am  Session 2 - Pitfalls or Challenges of New Payment Models
         Bruce Pyenson, Milliman
10:00 am – 10:15 am  Break
10:15 am – 11:00 am  Session 3 - Oncology Medical Home – A Patient-Centric System
          for Delivering Quality Cancer Care
          Barbara L. McAneny, MD, American Medical Association
11:00 am – 11:45 am  Session 4 - FDA on Testing and Personalized Medicine
          Speaker TBD
11:45 am – 12:15 pm  Session 5 - Revamping Research
          Raju Kucherlapati, PhD, Harvard Medical School
12:15 pm – 1:15 pm  Networking Lunch in Exhibit Hall or Sponsored Lunch Presentation
1:15 pm – 2:00 pm  Session 6 - Keynote Session - Value-Based Cancer Care:
          How Do We Get There in the ‘Omics Era?
          Gary Palmer, MD, JD, MBA, MPH, Nanthealth
2:00 pm – 2:45 pm  Session 7 - Can We Afford Personalized Medicine?
          Michael Kolodziej, MD, Aetna
2:45 pm – 3:30 pm  Session 8 - The Precision Medicine Initiative: Deliverables
          from Those on the Front Lines of Personalizing Care
          Harold Varmus, MD, National Cancer Institute (Invited)
3:30 pm – 4:15 pm  Session 9 - Adapting Regulation to Meet the Needs of the
          Exponential Growth of the Molecular Testing Era
          Victoria Pratt, MD (Invited)
4:15 pm – 5:00 pm  Session 10 - Role of Pathologist in the Age of Personalized Medicine
          Pranil Chandra, DO, PathGroup (Invited)
5:00 pm – 5:45 pm  Session 11 - The Role of Immunotherapy in Personalizing Treatment
          James Allison, PhD, MD Anderson Cancer Center (Invited)
5:45 pm – 6:00 pm  Poster Award Q & A
6:00 pm – 6:15 pm  Closing Remarks
6:15 pm – 8:15 pm  Reception in Exhibit Hall

*Agenda subject to change.