ONCOLOGY

Three Topical Treatments for Periocular and Conjunctival Malignancies

BY ANNIE STUART, CONTRIBUTING WRITER
INTERVIEWING BITA ESMAELI, MD, AND ANN P. MURCHISON, MD, MPH

For most eyelid and conjunctival neoplasms, the gold standard treatment remains complete surgical resection, using either frozen-section control of tumor margins or Mohs micrographic surgery—a precise, systematic excision of skin cancers that minimizes damage to surrounding healthy tissue. However, topical therapies may offer an alternative in cases where patients:

- are unwilling or too sick to undergo surgery;
- are immunosuppressed or have a genetic syndrome predisposing them to multiple malignancies, making surgical treatment impractical;
- have superficial but diffuse involvement of large areas of conjunctiva or eyelid skin; or
- need adjuvant therapy to help prevent recurrence.

Superficial tumors, for example, may affect a large area of the ocular surface, said Bita Esmaeli, MD, professor of ophthalmology at the University of Texas' MD Anderson Cancer Center in Houston. "Examples would include in situ melanoma of the conjunctiva or sebaceous carcinoma of the eyelid with pagetoid intraepithelial neoplasia. In some cases, removing the entire area of involvement can lead to severe limbal stem cell loss or significant scarring and ocular morbidity, greatly reducing visual function. That's when these drugs might come into play, but they certainly don't replace surgery for invasive melanoma or carcinoma."

Success rates of topical therapies don't match those of surgery, added Ann P. Murchison, MD, MPH, assistant professor of ophthalmology at Wills Eye Institute in Philadelphia. "But they're starting to be used more for cutaneous malignancies, and short-term response rates for some periocular lesions are promising."

Biopsy: First Things First

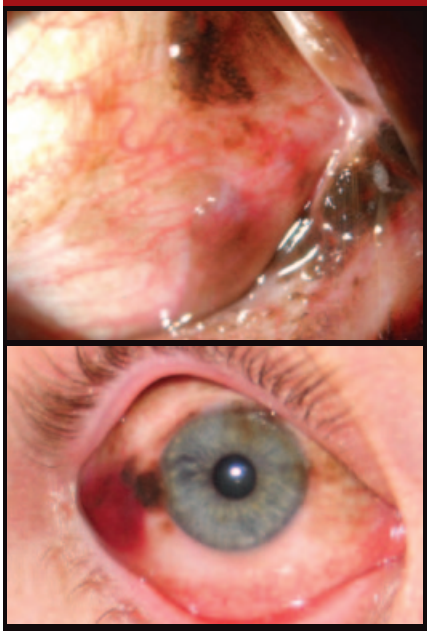
If considering the use of topicals, said Dr. Esmaeli, clinicians first need to ask, "Do I know what I am treating?" And the best way to answer that is with a biopsy. "I've seen really bad cases of advanced cancer because the practitioner didn't do a biopsy."

In most cases, the best approach may be to do an excisional biopsy, in which case topical chemotherapy may become moot. An example would be a well-circumscribed, bulbar conjunctival melanoma involving a limited area of the bulbar conjunctiva. For eyelid lesions, a biopsy is essential, especially when features like these are present:

- Ulceration or induration
- Asymmetry or irregular borders
- Telangiectasia
- Loss of eyelashes
- Discoloration
- Pearly borders
- Recurrent bleeding and scabbing

Chalazion or cancer? Periocular tumors can easily be mistaken for something else, causing a delay in diagnosis and treatment and leading to devastating effects, said Dr. Murchison.

Not a Small Problem



Examples of conjunctival melanoma involving large areas of the ocular surface and periocular tissue.

For example, sebaceous carcinoma can mimic chalazion, blepharoconjunctivitis or superior limbic keratoconjunctivitis. And this cancer's characteristic pagetoid spread or dermal infiltration may confuse clinician and pathologist alike. Unfortunately, these tumors can have widespread local and distant metastases.[1] "Many general ophthalmologists will do an incision and drainage of a chalazion without sending the contents for a histologic exam," said Dr. Esmaeli. "But given the availability of health care in developed nations and the relatively low cost of

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routine histologic evaluations, there's no reason that this tissue should not be sent to a path lab." And with skin cancers being a third of new malignancies, and the incidence of both periocular and conjunctival cancers increasing, caution is in order, she said.

Biopsies must be done carefully. Accurate tumor typing is critical because various periocular tumors can behave very differently, and the exact type of cancer impacts the treatment options. When rare cancers of the ocular surface and periocular region are suspected, an ophthalmologist might consider referral to a tertiary care center, even before biopsy, said Dr. Esmaeli. "We burn bridges sometimes by trying to do the preliminary steps before referral. If the biopsy is not done right, we lose information and are forever trying to make up for that."

With melanocytic lesions—primary acquired melanosis with atypia or invasive melanoma of the conjunctiva—it's especially important to handle the biopsy specimen properly, said Dr. Esmaeli. "That's because these are small specimens and the conjunctiva has the tendency to curl up around the edges. The specimen is also at risk of getting cut tangentially, which means we lose the opportunity to know whether or not it is invasive and to know the depth of invasion.[2,3] This is important in determining prognosis and selecting patients for additional diagnostic procedures, including sentinel lymph node biopsy." (For a related story, see Dr. Esmaeli's article "Sentinel Lymph Node Biopsy for Conjunctival and Eyelid Cancers," in February's *EyeNet* at www.eyenetmagazine.org.)

Whether the surgeon is removing the entire tumor or taking a smaller suspicious sample, said Dr. Esmaeli, it's essential to flatten out the conjunctival or eyelid specimen, to orient it precisely, and to communicate directly with the pathologist, sharing information about the margins of interest.

Top Candidates for Topical Treatment

When it comes to efficacy of topical treatments, the best evidence is for precancerous lesions, such as actinic keratoses, said Dr. Murchison. However, smaller and more superficial lesions, such as basal cell carcinomas, which account for 80 to 90 percent of eyelid tumors and tend to be locally destructive, are amenable to topical treatment, she said, and may be combined with other modalities. In certain cases, squamous cell and sebaceous carcinomas, as well as acquired melanosis and melanoma, may also benefit.[1,4] Here are descriptions of three useful agents:

5-fluorouracil (5-FU). FDA-approved for superficial basal cell carcinoma, 5-FU is a chemical ablative used for a range of dermatologic conditions. For cutaneous lesions, it may be combined with other modalities such as curettage or cryotherapy. In certain cases, such as with noninvasive squamous cell carcinoma of the conjunctiva, 1 percent 5-FU may be preferred to other topicals due to a lower incidence of serious side effects and lower costs to the patient.[5] Although 5-FU has been found safe and effective for this type of cancer, long-term follow-up is required due to possible recurrence.[6]

"Topical 5-FU doesn't replace surgical intervention, but it may play a role for biopsied lesions that may have an in situ residual component remaining at the edges or where doing a full-thickness corneal resection would cause vision problems and the risk of introducing the tumor into the eye," said Dr. Esmaeli.

Not commercially available, 5-FU eyedrops are mixed by compounding pharmacies. As a solution or cream, 5-FU is available as Efudex. However, this is used less often in the periocular region due to the local irritation it can cause.

Imiquimod. An imidazoquinoline, imiquimod (Aldara) is an immune-response modifier with potent antiviral and antitumor activity, and it is sometimes applied as a 5-percent cream for eyelid tumors.[7] In addition to being FDA-approved for actinic keratosis and warts, it is approved for some superficial basal cell carcinomas. It has also been used for squamous cell carcinoma and melanoma in situ, said Dr. Esmaeli, in particular for superficial in situ melanomas of the lentigo maligna variety, involving large areas of the periocular skin where a big surgery and reconstruction would otherwise be necessary.

Applied topically over a 6- to 12-week period, imiquimod creates an intense immune reaction, which can cause a lot of irritation on the skin and ocular surface, she said. "For this reason, it takes a particularly motivated patient to successfully complete treatment with topical imiquimod. However, once the area heals, more than 70 percent of patients with lentigo maligna melanoma in situ experience a near complete response."

Mitomycin C. With potent antitumor, antibiotic activity, mitomycin C is sometimes used, especially for the most aggressive of eyelid epithelial tumors and for conjunctival melanoma. "For sebaceous carcinoma with pagetoid spread on large areas of the conjunctiva," said Dr. Esmaeli, "topical mitomycin C offers a nice alternative to drastic radical surgery." That's because surgery may require removal of large areas of the upper and lower eyelid or conjunctiva and possibly even removal of the eye and orbital contents due to a diffuse but widespread involvement of the ocular surface. Melanocytic lesions and ocular surface squamous neoplasia of the conjunctiva may also benefit from mitomycin C, although a biopsy is critical to confirm the absence of invasive cancer.

Protocol, Side Effects and Follow-Up

Because these are fairly new agents as topical antineoplastics, the protocols for administration are varied, said Dr. Murchison. For example, "Some physicians will have patients use imiquimod once a day as a topical treatment and others will have them use it once a week. The duration of use is tailored to each patient."

A typical protocol for squamous cell carcinoma in situ, for another example, might involve using 5-FU eyedrops several times a day in short cycles, said Dr. Esmaeli. "I prefer to use them four times a day for four days." She then

inserts a 10-day drug holiday between cycles to give the eye time to recover.

Irritation is common. The main side effect of topical 5-FU is ocular surface irritation. It can also cause problems with dry eye symptoms and redness, and, in very rare cases, corneal abrasion. Topical mitomycin C can similarly cause ocular surface irritation, as well as dry eye and some problems with tear drainage, added Dr. Esmaeli. Imiquimod causes a fairly significant skin reaction. "If it gets into the eye and if it is applied too close to the eyelid margin, it can cause conjunctivitis and keratopathy," said Dr. Murchison.

Follow-up is key. Potential side effects like these are one reason patients who are treated with topical chemotherapy should be followed frequently, said Dr. Murchison.

"For most of these cancers, we typically follow the patient every three months after completion of surgical treatment or adjuvant topical chemotherapy during the first year, every six months during the second year, and then perhaps have longer intervals thereafter up to five years," said Dr. Esmaeli. "During each visit, we'll be looking for local recurrence and, in some cases, metastases, keeping a close eye on regional lymph nodes, especially for patients with invasive conjunctival or eyelid melanoma, sebaceous carcinoma or larger squamous cell carcinomas of eyelid or periocular region."

Drs. Esmaeli and Murchison report no related financial interests.

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