 Conjunctival melanoma is a rare condition that can threaten not only vision but life as well. Historically, treatment has been primarily surgical, with advanced cases requiring highly aggressive procedures such as orbital exenteration. With a lack of clinical trial data, management methods vary between clinicians and institutions, with a potential role for other therapies such as topical chemotherapy or radiotherapy as adjuvant or even primary treatments in certain settings. However, systemic medications are now emerging as a treatment option that may reduce the need for surgery and dramatically shift the approach to management.

In this two-part roundtable, Lauren A. Dalvin, MD, at Mayo Clinic in Rochester, Minnesota, leads a discussion with Bita Esmaeli, MD, at The University of Texas MD Anderson Cancer Center in Houston, and Richard D. Carvajal, MD, at the Northwell Health Cancer Institute in New York. This month, Part 1 takes a look at these emerging systemic options: how can they best be used to safely preserve the eye and minimize the risk of metastasis? Part 2 continues next month.

Disease Characteristics

**Dr. Dalvin:** Many of the systemic drugs that are being tried for conjunctival melanoma are repurposed from cutaneous melanoma. How similar are these conditions?

**Dr. Esmaeli:** There are similarities between them in terms of clinical behavior and patterns of metastasis. Conjunctival melanoma is much more similar to cutaneous melanoma than it is to uveal melanoma.

For example, as with cutaneous melanoma, regional lymph nodes are the most common initial metastatic target for conjunctival melanoma. However, it’s estimated that about a quarter of cases of conjunctival melanoma can have distant hematogenous metastasis even without lymph node metastasis, and that pattern is somewhat analogous to cutaneous melanoma. Even some of the significant prognostic pathologic parameters—for example, tumor thickness and ulceration—are similar between the two conditions.

**Dr. Carvajal:** I agree that conjunctival melanoma is closer to cutaneous than to uveal melanoma, but I think of it as a disease entity lying somewhere between mucosal and cutaneous melanoma. Although the conjunctiva is a mucosal surface, it is unlike other mucosal melanomas, which arise from sun-protected areas of the body, such as the nasosinal surfaces, the vulva/vagina, and anal/rectal areas.

The conjunctiva—at least the bulbar portion—is exposed to UV radiation. Thus, unlike other mucosal melanomas, which have a relatively low mutation burden, conjunctival melanomas are more heavily mutated, akin to cutaneous. As in cutaneous melanoma, we can see mutations in *BRAF*, *NRAS*, or *NF-1* in conjunctival melanoma (although less frequently than in the cutaneous form). As in mucosal melanoma, we can also see cases driven by alterations in *KIT*.

**Dr. Dalvin:** These are important points, and I want to summarize them because in the world of ophthalmology, it’s tempting to artificially lump ocular melanomas into one group. We need...
to distinguish conjunctival melanoma from uveal melanoma, which is more likely to be associated with GNAQ and GNA11 mutations and doesn’t have strong links to UV radiation exposure.

And, as Dr. Esmaeili said, the metastatic pattern of conjunctival melanoma is one that most commonly spreads to the lymph nodes, whereas uveal melanoma most commonly spreads hematogenously to the liver. Thus, the medications that we think may potentially be effective for conjunctival melanoma might not be helpful for uveal melanoma.

**Advances in Systemic Therapy**

**Dr. Dalvin:** The similarities between cutaneous and conjunctival melanoma raise the possibility that some drugs might work in both of these cancers. What are some of these systemic medications, and how do they work?

**Dr. Carvajal:** Every time I talk about treating advanced disease, I’m always struck by how we are in such a better place than when I started. About 20 years ago, all we really had was chemotherapy; but since 2011, 14 therapies or regimens have been approved for cutaneous melanoma, and they are not chemotherapy-based. Instead, they are immunotherapies such as novel checkpoint inhibitors as well as targeted therapies. So now when I talk to patients with advanced unresectable disease—cutaneous or conjunctival—I’m frequently talking about immunotherapy as the frontline therapy, with targeted therapy in some cases as a next-line option.

Broadly speaking, when we use immunotherapy, we’re treating patients with something that will alter or facilitate the ability of the immune system to recognize the cancer and eliminate it. That’s what these antibodies to PD-1, CTLA-4, or LAG-3 are doing: facilitating the immune response against cancer. In cutaneous melanoma, we’re curing 40% to 50% of patients with advanced disease, even with liver or brain metastases. The response rates we can achieve in mucosal melanoma with these therapies are lower than what we see with cutaneous disease. Because of the rarity of conjunctival melanoma, we don’t have large data sets, but I would expect the response rates we achieve in conjunctival melanoma to be between what we see with mucosal and cutaneous disease.

The other form of therapies that we use more frequently now are the targeted therapies; the approved regimens targeting the MAP kinase pathway that can be activated by BRAF mutations. If we shut down that pathway with various inhibitors, we can get really good responses, whether it’s a cutaneous, mucosal, or conjunctival melanoma.

**Dr. Dalvin:** What are the names of some of the medications we’re talking about?

**Dr. Carvajal:** Typically, the approved immunotherapies for melanoma are the checkpoint inhibitors, anti–PD-1 antibodies like pembrolizumab or nivolumab. Ipilimumab is the anti–CTLA-4 antibody, and now we also have LAG-3 targeted therapies—relatlimab, which is administered together with nivolumab. For the MAP kinase targeted therapies now, we always use two agents: a BRAF inhibitor plus a MEK inhibitor. These combinations include dabrafenib and trametinib, encorafenib and binimetinib, and vemurafenib and cobimetinib.

**Clinical Use: Surgery, Medical Therapy, or Both?**

**Dr. Dalvin:** How are these medications actually being used in the clinic? What kind of patient are they best suited for?

**Dr. Esmaeili:** The majority of small or medium bulbar conjunctival melanomas can be managed with local treatment—primarily surgical resection, and in some cases other modalities such as topical mitomycin or radiation—which can preserve fairly decent function of the eye and establish relatively good short-term local control rates, but we still have a high rate of local recurrence. In most centers, a 20% to 30% recurrence rate is considered acceptable. In some scenarios, I would consider systemic therapy. These may include:

**Repeated recurrences.** For example, some patients come back over the years with relatively thin but diffuse conjunctival melanomas that are perhaps growing toward the cornea. In such cases we used to just operate and operate and operate again, which caused scarring, loss of function, and perhaps restriction of the extraocular muscles. I have used PD-1 inhibitor therapy in this scenario, and this approach can work nicely and may avoid repeated surgery.

However, it’s an off-label use, and you need to discuss it with medical oncologists who are familiar with the topic and who think a bit outside the box because these patients don’t have metastasis. But they are at risk for ocular morbidity if they continue to have recurrences and surgery. By using immune checkpoint inhibitor therapy, we hope to attain durable local control and avoid multiple surgeries.

**Extensive surface involvement.** Another scenario would be in patients where the entire ocular surface is involved or where the tarsal and palpebral conjunctiva in the upper and lower eyelids plus multiple quadrants of the bulbar conjunctiva are involved. For these patients, the only curative surgical option would often be an orbital exenteration.

With orbital exenteration, patients experience the loss of the eye but also would have a significant facial deformity. Orbital exenteration has a big impact on the patient’s quality of life. So, as surgeons we want to deliver eye-sparing surgery and decrease surgical morbidity as much as possible, and immune checkpoint inhibitors could make a difference in such patients.

**Presence of metastasis.** The third scenario would involve patients who already have regional lymph node metastasis or distant metastasis at the time of presentation with the conjunctival melanoma. These patients may be better candidates for immunotherapy up front, with surgery used as salvage for whatever residual melanoma remains on the eye; a recent patient who had lung metastasis and recurrent conjunctival melanoma comes to mind. There’s a compelling case for using the drugs up front for the metastatic lesion but also to see if the conjunctival lesion also may respond, which could mean potentially less surgery and less ocular morbidity. Then perhaps you do a small biopsy to show that what’s left is just...
benign pigment rather than residual melanoma.

In addition, immune checkpoint inhibitors could be considered for patients who don’t have a local recurrence in the eye area but develop nodal or distant metastasis during the surveillance period. Sometimes nodal or distant metastasis is not apparent until after a year or two, or even many years after treatment for the primary conjunctival lesion.

In all of these scenarios, communication between the ophthalmologist and the medical oncologist is really important to get them engaged and to get them to consider judicious use of immune checkpoint inhibitor or targeted therapy for patients with conjunctival melanoma.

**Neoadjuvant and Adjuvant Therapy**

**Dr. Dalvin:** What do the terms neoadjuvant and adjuvant therapy mean, and how are we using these therapies in conjunctival melanoma?

**Dr. Carvajal:** These terms are defined by the timing of therapy in relation to surgery. Any sort of treatment given before surgery is called a neoadjuvant therapy and any therapy given afterward is called an adjuvant therapy. The use of adjuvant therapy in high-risk cutaneous melanoma is well established. For cutaneous melanoma, we know that if we give a course of adjuvant immunotherapy with a single-agent anti-PD-1 therapy, or, if the tumor has an activating BRAF mutation and we do a year of targeted therapy, we reduce the risk of recurrence by approximately 40%. So, adjuvant therapy is something that we routinely offer to our patients with high-risk cutaneous melanomas.

One of Dr. Esmaeli’s colleagues, Sapna P. Patel, MD, published a really important paper in the *New England Journal of Medicine* last year. The SWOG (Southwest Oncology Group) 1801 trial looked at the use of neoadjuvant immunotherapy in cutaneous melanoma.¹ In this trial, patients were randomized either to surgery first followed by 18 doses of pembrolizumab over about a year (adjuvant-only group) or to three doses of pembrolizumab before surgery plus 15 doses afterward (neoadjuvant-adjuvant group). One of the main questions was, if we start immunotherapy when clinically evident tumor is in place, is there a difference in outcomes when compared with starting immunotherapy following resection?

The data were strikingly positive in favor of neoadjuvant therapy. At two years, the event-free survival in the neoadjuvant-adjuvant group was 23 percentage points better than in the adjuvant-only group (72% vs. 49%, respectively). It shows how the presence of intact tumor allows the immune system to more effectively recognize the melanoma-associated antigens to achieve a more effective response.

**Weighing Risks vs. Benefits**

**Dr. Dalvin:** How might these findings apply to conjunctival melanoma?

**Dr. Carvajal:** It’s very important to highlight that we don’t have a great deal of data regarding the role of adjuvant or neoadjuvant therapy in mucosal melanoma, and this is even more the case in conjunctival disease. How do we define high-risk characteristics for this disease? Does a 20% risk of recurrence locally, regionally, or distantly warrant neoadjuvant or adjuvant therapy? Or does a higher or lower risk warrant therapy?

As you can imagine, patients are always burdened with a concern that their cancer will recur and do consider the risks and benefits of neoadjuvant or adjuvant therapy. The issue is that there are side effects, some of which can be permanent. About 20% of patients treated with adjuvant anti-PD1 therapy will develop a permanent endocrinopathy—they might lose thyroid function, adrenal function, or pituitary function. Is that risk worth the potential benefit? It’s essential to weigh the risks and benefits for the patient.

I think that considerations in the neoadjuvant setting may be different, especially in a case where the only potential curative surgery will cost the patient their eye. What if you could preserve the eye? In that setting, you can imagine saying, “Let’s do a trial of neoadjuvant therapy.” We might be able to achieve some degree of disease control and maybe downstage the tumor to make it more easily resectable. And potentially, we might not even need to do the surgery. I think that’s a really, really compelling space to think about using systemic therapy.

**Dr. Esmaeli:** I agree 100% with Dr. Carvajal, but I’d like to add my perspective as a treating surgeon. For me, the cases that are really compelling for using a neoadjuvant are those that are headed for an orbital exenteration or that have such a large bulbar melanoma that removing it will cause extraocular muscle restriction or other permanent morbidity for the eye.

In the 19 cases in my practice that we have treated with this approach thus far, the response rate was close to 70%. These cases were all locally advanced, recurrent, and some also had metastatic disease. So, I think we can expect a good response rate in patients with conjunctival melanoma similar to expected response rates for patients with cutaneous melanoma, but of course some patients will not respond. And there are some risks. One is that if you delay surgery in a case that is surgically resectable, you could risk further progression of melanoma in the eye area. Second, side effects from drug therapy are a concern, as Dr. Carvajal mentioned. A third concern is that we still are learning and making observations about how long it takes to achieve a response; meaning how many cycles of drug therapy are enough to achieve a local response in the eye area.

Unlike the periorcular cutaneous squamous cell carcinomas and ocular surface conjunctival squamous cell carcinomas, which respond to immunotherapy rather quickly, the clinical response appears to be slower in patients with conjunctival melanoma, at least in my experience. For example, in a case I published in *Ophthalmic Plastic and Reconstructive Surgery* a few years ago, I reported on a patient who was headed to exenteration, with all the ocular surface and upper and lower eyelids involved.² It took several months of immunotherapy to see any change in pigmentation, but after a year, there was hardly any residual pigment left.

I biopsied the areas of residual pigment and they were benign. You can
actually see the photographs to appreciate this—there is a photographic diary of this patient in the publication. We now have several years of follow-up for the patient described in the publication, and she has had a durable response and still is doing great.

**Challenge: Lack of Trial Data**

**Dr. Esmaeli:** I’d like to comment on the difficulty of carrying out prospective trial research in patients with conjunctival melanoma. Conjunctival melanoma is a very rare disease compared with cutaneous melanoma or even uveal melanoma. Because of the small number of patients, we are limited to retrospective case series and anecdotal observations rather than clinical trials.

Since these immunotherapy drugs became available, we have used them to treat 19 conjunctival melanoma patients at my institution. The regimens included the PD-1 inhibitors, sometimes as single therapy or, initially, in combination with CTLA-4 inhibitors followed by single-agent PD-1 inhibitors. We have published a few of these cases and will try to publish more, but it’s difficult to get these reports accepted by journals because they’re considered anecdotal experience, and it is difficult to have high-impact journals publish small case series. In the world of ocular therapy at large, anecdotal experience may not be viewed as important, but in our world of ocular oncology they do contribute significantly to our understanding of options for patients with conjunctival melanoma.

Dr. Dalvin, you recently edited a special issue of the *Canadian Journal of Ophthalmology* dedicated to ocular oncology, where you invited people to publish these sorts of rare observations. I applaud your work on this; sharing and bringing together our unique expertise so we can learn from each other is important to advance our understanding of conjunctival melanoma.


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