The Fundamentals of Uveal Melanoma

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Epidemiology and Prognosis

Uveal melanoma represents 5%–6% of all melanoma diagnoses (Bedikian, 2006). The most important factor in the development of uveal melanoma is the presence of congenital ocular melanocytosis. This condition manifests as a gray-brown pigmentation in the periorcular region, temporal fossa, palate, sclera, uvea, orbit, and meninges (see Figure 2). Caucasian individuals with this condition carry a 1 in 400 lifetime chance for the development of uveal melanoma. Other risk factors include the presence of a choroidal nevus, light eye color, fair skin, and inability to tan (Shields & Shields, 2009).

Survival rates for uveal melanoma remain poor. Intraocular location of a uveal melanoma also can affect a patient’s prognosis for metastasis. Tumors confined to the iris carry the most favorable prognosis, followed by those in the choroids. Ciliary involvement carries the least favorable prognosis.

Tumor size (primarily largest tumor diameter) continues to be the dominant predictor for metastasis (American Joint Committee on Cancer, 2002). Choroidal melanomas are routinely classified by height and diameter as small, medium, or large (see Table 1). A small tumor at diagnosis carries a more favorable prognosis than a medium or large tumor (Bell & Wilson, 2004). Advances made in the treatment of the primary tumor have not resulted in any improvement in survival rates. As many as 50% of patients will develop metastatic disease, even 10–15 years after diagnosis, which invariably leads to death (Triozzi, Eng, & Singh, 2008). At the time of diagnosis, 99% of patients have disease limited to the eye, but at least 30% will die of systemic metastases at five years and 45% at 15 years. The liver is involved in up to 95% of individuals who develop metastatic disease. Despite current therapy, the median survival of patients who develop metastases is reported to be about six months, and the one-year survival is estimated to be 10%–15% (Bedikian, 2006). Systemic monitoring twice yearly with physical examination and liver function tests and annual liver imaging and chest radiograph is advised (Sato et al., 2008).

Diagnosis

Most melanomas are dome-shaped, with the tumor thickness about 50% of the basal dimension. Choroidal melanoma manifests as a brown or, less commonly, yellow mass deep in the retina and typically with secondary retinal detachment. Vitreous hemorrhage or secondary glaucoma can occasionally develop (Shields & Shields, 2009). Patients are frequently asymptomatic; however, they may complain of visual changes progressing to symptoms of retinal detachment.

The most reliable way to make the diagnosis of choroidal melanoma is with the use of indirect ophthalmoscopy, followed by those in the choroids. Ciliary involvement carries the least favorable prognosis. Tumor size (primarily largest tumor diameter) continues to be the dominant predictor for metastasis (American Joint Committee on Cancer, 2002). Choroidal melanomas are routinely classified by height and diameter as small, medium, or large (see Table 1). A small tumor at diagnosis carries a more favorable prognosis than a medium or large tumor (Bell & Wilson, 2004). Advances made in the treatment of the primary tumor have not resulted in any improvement in survival rates. As many as 50% of patients will develop metastatic disease, even 10–15 years after diagnosis, which invariably leads to death (Triozzi, Eng, & Singh, 2008). At the time of diagnosis, 99% of patients have disease limited to the eye, but at least 30% will die of systemic metastases at five years and 45% at 15 years. The liver is involved in up to 95% of individuals who develop metastatic disease. Despite current therapy, the median survival of patients who develop metastases is reported to be about six months, and the one-year survival is estimated to be 10%–15% (Bedikian, 2006). Systemic monitoring twice yearly with physical examination and liver function tests and annual liver imaging and chest radiograph is advised (Sato et al., 2008).

Although rare, uveal melanoma is the most common primary intraocular malignant tumor in adults. Over the past 50 years, the incidence in North America has been stable, with 4.3 per million (or about 1,500 cases per year) being newly diagnosed (Sato, Han, & Yamamoto, 2008). Uveal melanoma differs from cutaneous melanoma in a variety of ways, such as primary treatment, metastatic pattern, and overall chemoresistance. Many of the classic chemotherapeutic regimens used in metastatic skin melanoma, such as dacarbazine or high-dose bolus interleukin-2, are ineffective when used in metastatic uveal melanoma. This article will review primary uveal melanoma.

Anatomy

The four tissues in the ocular region can give rise to primary melanoma, including the uveal tract, conjunctiva, eyelid, and orbit. The uvea is a vascular layer within the eye that is divided into the three anatomic compartments of the iris, ciliary body, and choroid (see Figure 1). Uveal melanoma is by far the most common of the ocular melanomas, and orbital melanoma is the least common (Shields & Shields, 2009). The iris is the most anterior portion of the uveal tract. It divides the anterior segment of the eye into the anterior and posterior chambers and is bathed by aqueous on both sides. The choroid, the most posterior part of the uveal tract, extends from the optic nerve to the ora serrata and is the pigmented vascular layer of the uveal tract that maintains the retina. Its primary function is to provide oxygen and nourishment to the outer retinal layers. The ciliary body is a ring-shaped structure when viewed from the front of the eye (Modi & Edward, 2008).

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coherence tomography, autofluorescence, and fine needle aspiration biopsy are helpful ancillary procedures (Shields & Shields, 2009). Cytogenetic analysis of melanoma has revealed mutations most often in chromosomes 1, 3, 6, and 8. Chromosome 3 abnormalities, particularly monosomy 3, carry a poor prognosis, with about 95% metastasis by five years (Modi & Edward).

Treatment

When localized uveal melanoma is diagnosed, two treatment options generally are offered. Radiotherapy, in the form of brachytherapy using a radioactive iodine 125 plaque, is the most commonly used for small or medium lesions. The radioactive plaques can be custom designed to treat uveal melanoma at any site within the uveal tract (Shields & Shields, 2009). The other treatment option is oculocutaneous. This is generally indicated for advanced melanomas that occupy most of the intraocular structures and for those that have produced secondary glaucoma. A prosthesis is later fitted with an excellent cosmetic appearance (Shields & Shields).

Despite advances in diagnosis and management of primary uveal melanoma, systemic uveal melanoma metastases are difficult to treat. Metastasis is by vascular spread, and about 40%–50% of patients with primary uveal melanoma will ultimately develop metastases. The management of metastatic uveal melanoma is dependent on whether metastatic disease is confined to the liver. The presence of hepatic metastasis is associated with poorer survival, with an average median survival of only six to eight months (Bedikian, 2006). Other sites of metastasis include the lungs and skin; however, disease occurs less frequently in these sites (Shields & Shields, 2009).

Local treatments are frequently the option of choice for patients with metastatic uveal melanoma (see Figure 3). Local treatments such as surgical resection or radiofrequency ablation aimed at controlling liver metastases could be considered for the management of this otherwise highly chemoresistant tumor. However, the major limiting factors for surgical or ablative treatments are presence of too many metastatic foci or large masses, tumors in difficult locations, tumors invading blood vessels, and insufficient hepatic reserve (Bedikian, 2006).

Hepatic chemoembolization is a frequently used treatment option when the patient is not a candidate for these options. Chemoembolization is the use of a chemotherapy agent (carmustine or cisplatin) that is directly injected into the tumor to stop blood flow and introduce a cytotoxic agent directly into the tumor (Bedikian, 2006). Immunoembolization is a similar procedure to chemoembolization; however, granulocyte macrophage-colony-stimulating factor is used instead of cytotoxic chemotherapy (Bedikian). Hepatic arterial chemotherapy infusion is the introduction of high-dose chemotherapy directly into the arterial circulation. Hyperthermic isolated hepatic perfusion is designed to expose the liver to high doses of chemotherapy or immunotherapy to achieve maximal tumor shrinkage. This procedure requires a lengthy operation for multiple catheter placement for the instillation of chemotherapy and/or tumor necrosis factor (Bedikian). These options require a significant amount of technical expertise, and their unequivocal survival benefit has yet to be determined.

Systemic Therapies

Uveal melanoma is widely considered to be a chemotherapy-resistant cancer. Retrospective reviews from several well-respected groups indicated that the response rates to drugs commonly used for the treatment of metastatic cutaneous or mucosal melanoma rarely induced responses in patients with uveal melanoma, particularly when the liver was involved with metastatic disease (Bedikian, 2006). Biotherapy, interleukin-2, and interferon alfa-2b has had limited evaluation for efficacy against metastatic uveal melanoma.

Investigative Therapies

The focus of current research and potential treatment options are primarily in the targeted therapy arena. Targeted therapeutics address molecular abnor-
malities that are associated with tumor development and progression (Triozzi et al., 2008). Several pathways have been found to be involved in the progression of uveal melanoma, representing opportunities to halt the progression of this disease. Among those, upregulation of c-kit, c-Met, and insulin-like growth factor receptor 1 are considered to be the most important potential molecular targets (Sato et al., 2008). Uveal melanoma spreads preferentially to the liver, and an altered insulin-like growth factor receptor 1 and c-Met expression in uveal melanoma may act to enhance cell growth and tumor progression (Economou et al., 2008).

Nursing Implications

Nurses working with patients with uveal melanoma are frequently challenged by a variety of patient-related issues. Patients will require emotional support throughout the disease trajectory. This disease trajectory may be long, and the development of metastatic disease may occur many years after the initial diagnosis of localized disease.

After initial diagnosis and treatment, which may be with radiopaque plaque placement or ocular enucleation, patients will have changes in their vision. These changes may vary from mild blurry vision in the affected eye to accommodation of vision with only one eye. Patients may require counseling by occupational therapists or nurses with specialized training on visual accommodation exercises and tips on how to accommodate their visual changes to their activities of daily living, such as driving.

In addition, patients should be educated on possible drug side effects, drug toxicities, and procedures that may be performed.

The importance of follow-up imaging studies, laboratory studies, and physician appointments should be stressed to patients. Surveillance studies and schedules will vary from facility to facility; however, they should include a liver function profile and imaging of the liver because this is the most frequent site of metastasis. Early detection of metastatic disease is the goal of surveillance and will impact treatment options and survival.

Palliative care plays a crucial role in symptom management and/or end-of-life care. Unfortunately, many patients with metastatic uveal melanoma will eventually succumb to the disease, and the symptom burden can be considerable. Symptoms frequently observed are pain (particularly to the right upper-abdominal quadrant), anorexia, early satiety, shortness of breath, and altered mental status. Altered mental status can occur at the end of life secondary to liver failure. Liver failure is a common cause of death because the liver becomes replaced by diseased tissue, leading to liver failure.

Conclusion

Although rare, uveal melanoma is the most common intraocular tumor. Unfortunately, the prognosis remains poor, particularly when metastatic disease develops. Current therapeutic options for metastatic disease include local and systemic therapies with varying degrees of efficacy. Progress is being made in the development of targeted therapy drugs, and nurses should be ready to respond to patient education needs and symptom management concerns regarding metastatic disease.

| Table 1. Uveal Melanoma Tumor Size |
|-----------------|--------------------------------------------------|
| SIZE            | DESCRIPTION                                      |
| Small           | Less than 10 mm in diameter and less than 3 mm in height |
| Medium          | 10–15 mm in diameter and 3–5 mm in height         |
| Large           | More than 15 mm in diameter and more than 5 mm in height |

Note. Based on information from Bell & Wilson, 2004.

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