Retinoblastoma: A Review of Current Treatment Strategies

ABSTRACT: *Since the last review of retinoblastoma therapies in the Journal of Ophthalmic Prosthetics 15 years ago, there has been a significant shift in the approach to treating this disease. In the early 1990s, a group of investigators in Los Angeles, Toronto, and London began using chemotherapy to reduce the size of intraocular tumors in the hope of avoiding external beam radiation (EBR). The purpose of this STET in this article is to provide an update on the current therapeutic approaches to retinoblastoma and the future direction of work in this field.*

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HISTORICAL PERSPECTIVE

Retinoblastoma (RB) is a genetically determined tumor arising from the retinal cells of infants and preschool-aged children. Tumors result from a deletion of the retinoblastoma gene, located on chromosome 13, which codes for a protein that acts as an anti-oncogene or tumor suppressor. Loss of both alleles of this gene confers tumorogenesis. The loss of the alleles can occur shortly after fertilization, resulting in a germinal mutation that will be present in every subsequent cell. Loss of the alleles in a single retinal cell further along in embryogenesis results in a somatic mutation.

Germinal mutations typically result in earlier onset, multiple/bilateral tumors. Somatic mutations initially give rise to unifocal disease. Bilateral cases typically present at a younger age (one year or less); unilateral disease typically arises around the second birthday.

The presence of a germinal mutation, in which the RB protein is absent in every cell, makes the affected individual susceptible to radiation-induced tumorogenesis, specifically sarcomas. It has long been recognized that children with bilateral RB have a five-fold increase in risk of second malignant neoplasms (SMNs) after they are treated with EBR. It is this unfortunate phenomenon that has stimulated the work with chemotherapy.

RB arises in one of every 15,000-20,000 live births. Approximately one in three to one in four affected children will have a family history of RB. The survival rate in the United States and United Kingdom exceeds 90%. Unilateral disease is the most common form. Trilateral RB, a rare variant, is bilateral disease with tumor arising from primitive retinocytes in the region of the pineal gland.

The most common presenting symptom is leucocoria or abnormal papillary reflex, often noted by a family member several months prior to presentation to the ophthalmologist. Strabismus is common, especially in uni-

FIGURE 1 This pathology photograph shows the damage caused from retinastbloma. (Cross section)

lateral disease. Other signs/symptoms include loss of vision, red eye(s), and uveitis. RB rarely causes cataract.

Evaluation of children with a presumptive diagnosis of RB includes an examination under anesthesia, fundus photography, and radiologic studies of the brain and orbits.

ENUCLEATION

Enucleation remains the primary treatment for all but a few unilateral cases, that tend to present with advanced disease because of visual preservation in the normal contralateral eye. Advances in technique and porous implant materials have resulted in good motility, excellent cosmesis, and a very low extrusion rate. Patients

who receive chemotherapy shortly after enucleation may be at higher risk for infection and extrusion, however.

Enucleated globes are examined histopathologically for extraocular tumor extension and extension into the optic nerve. It is imperative that the enucleating surgeon take a long (10-cm) piece of optic nerve as tumor at the cut margin of the nerve imparts a poor prognosis. Finding tumor cells past the lamina cribrosa of the nerve (the exit point of the nerve from the globe) is an indication for prophylactic chemotherapy (see below).

In eyes treated initially with other eye-sparing modalities, there is always the risk of subsequent enucleation due to recurrence of tumor; blind, painful eyes developing secondary to complications of radiation, e.g., neovascular glaucoma; and disfigured globes due to the late effects of radiation or chronic retinal detachment.

RADIATION/EBR

EBR still plays a role in the management of retinoblastoma. Radiation is indicated in the face of diffuse vitreous seeding (Reese-Ellsworth stage 5B), failure of chemotherapy or other modalities, widespread recurrences, or intolerance of chemotherapy. The parent of children treated with radiation should understand that there is a significant risk (approximately 30% over 40 years) of the development of SMNs (sarcoma) within and outside the filed of radiation.

Local complications of EBR include facial deformities caused by the cessation of orbital bone growth, keratopathy and dry eye, cataract, and radiation damage to the retina and optic nerve resulting in visual loss. The latter can result in proliferative retinopathy, neovascular glaucoma, and severe vision loss.

PLAQUE BRACHYTHERAPY

Plaque brachytherapy is a safe alternative to enucleation in eyes with intraocular melanoma. However, localized radiation treatment in the form of isotope-impregnated episcleral plaques is used sparingly in eyes with RB. Large tumors in extramacular locations are suitable for this treatment.

The plaques, containing radioactive iodine-125, are sewn to the eye for two days to four days, allowing for radiation to the underlying choroid, retina, and tumor. Local complications include diplopia, cataract, and radiation retinopathy. In eyes treated previously or concurrently with chemotherapy, there is a very

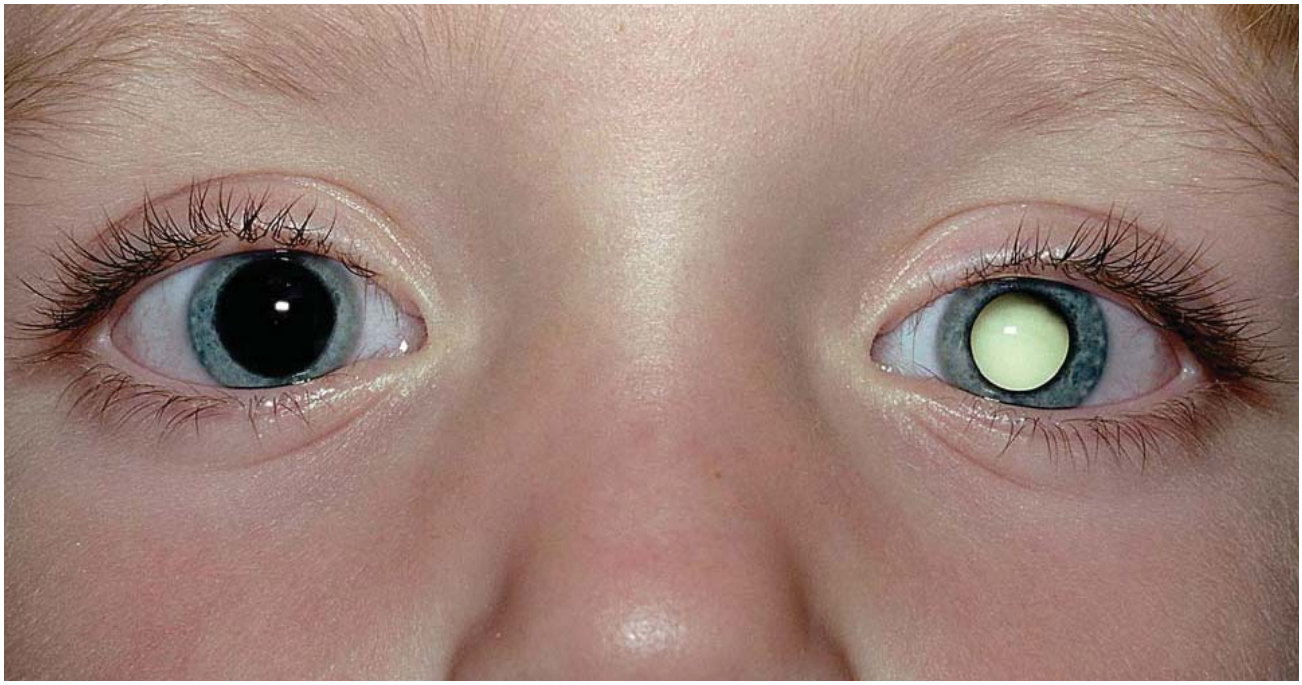

FIGURE 2 Tumor visible through dilated pupil in left eye.

high risk of radiation retinopathy, limiting the usefulness of this modality.

Photocoagulation/Cryotherapy

Cryotherapy is well-suited for small anterior (anterior to the equator) RB tumors. A triple freeze-thaw technique, in which the tumor is encased in a localized ice ball three times in rapid succession, is effective in causing immediate cell lysis and necrosis of tumor tissue. Cryotherapy can cause shrinkage of the sclera, and extensive treatment predisposes the developing eye to myopia and increases the risk of late retinal detachment.

Direct photocoagulation of small tumors is often used during chemotherapy or afterward for small recurrences or new tumors. The widespread availability of indirect ophthalmoscope laser delivery systems makes the application of laser energy to small posterior and anterior tumors easy, safe, and effective. The precise nature of the laser allows the treating physician to limit damage to the tumor and very little or none of the surrounding (normal) retina. Localized burns of the iris, particularly the papillary margin, are rare.

CHEMOTHERAPY

Early investigators of chemotherapy for RB used agents that were well known to their colleagues in oncology. The current protocol has changed little from the initial investigations at the Childrens Hospital Los Angeles developed in the early 1990s by A. Linn Murphree, M.D. The combination of etoposide phosphate, vincristine sulfate, and carboplatin is infused every four weeks, typically for six months. Complications of the drugs include neutropenia and infection, anemia, hearing loss, sensitivity to one or more of the agents, and later leukemia.

One of the remarkable features of chemotherapy is its ability to reduce the size of RB tumors and resolve tumor-associated retinal detachments. This phenomenon has been termed *chemoreduction*. The use of chemotherapy can often reduce the size of the initial tumor four- or five-fold, thereby limiting the collateral damage of any local treatment.

It was established early in the use of chemotherapy that these agents alone were not adequate to eradicate RB; a simultaneous local therapy was needed. Most cases are treated with simultaneous laser hyperthermia. Typically, tumors are heated with argon or diode laser a few hours before infusion of the chemotherapy. There is a synergistic effect of the heat with the drugs (particularly carboplatin) that allows for a high rate of tumor control and eradication. This technique is called *ThermoChemoTherapy* (TCT).

Small tumors in the posterior pole are ideally suited to TCT. The precision of laser treatment can limit damage to the tumor tissue alone, sparing nearby structures such as the fovea and optic nerve, thereby maximizing vision preservation.

Chemotherapy is not effective in treating diffuse vitreous seeding and tumor in the anterior chamber. Chemotherapy is indicated for children whose enucleated globes show features considered to impart a high risk of developing metastasis. These features include extraocular extension, tumor past the lamina cribrosa of the optic nerve, massive involvement of the choroids, and tumor in the anterior chamber. Patients with known metastases are also treated with chemotherapy. Metastases usually involve the central nervous system and bone marrow. The prognosis for survival from metastatic RB is poor.

FUTURE DIRECTIONS

Treating physicians agree that we must continue to evolve away from radiation. The remaining obstacle is the presence of diffuse vitreous seeds, for which EBR is our only proven and reliable option. Several investigators are working on intraocular drug delivery. A large depot injection of drug(s) in the episcleral or sub-Tenon's space may provide adequate intravitreal drug levels via a transcleral route.

The Childrens Oncology Group has established a protocol for a prospective series of studies of treatments for intraocular and metastatic RB. Those results will continue to refine the clinical approach to RB. Work at Childrens Hospital Los Angeles and elsewhere has identified specific RB cell lines. Future approaches to tumor control may include treatments tailored to specific cell lines.

Screening at-risk children, e.g., those with a family history of RB, remains a vital tool in preventing visual loss from RB. At-risk children should be screened shortly after birth and regularly through the

FIGURE 3 Normal eye.

first two years of life. Any report of abnormal papillary reflexes in a preschool-aged child requires immediate referral to a pediatric ophthalmologist for a dilated funduscopic examination.

Finally, good follow-up care and support are critical for affected children to maintain functionality, productivity, and self-esteem. Every professional who encounters an affected child during the course of his or her treatment has the capacity to soothe, reflect positively, and encourage that child to overcome a difficult and often traumatic condition.

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