

ONCOLOGY

Retinoblastoma, Part Two: Secondary Neoplasms in Older Children

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Retinoblastoma has been transformed from a deadly childhood cancer to one that is largely curable—at least in the developed world, where access to retina and oncology specialists provide the comprehensive care that retinoblastoma calls for. Retinoblastoma is often diagnosed within the first two years of life, and its survival rate in the developed world is 99 percent; in fact, retinoblastoma treatment has achieved the highest survival rate of all pediatric cancers.¹ Of special interest to ophthalmologists: more than 90 percent of patients maintain normal vision in at least one eye.

Unfortunately, some of these children will be at increased risk later in life to face a second retinoblastoma or other cancer.

Saving Eyes as Well as Lives

Although enucleation is still a common treatment for this cancer, eye-preserving therapies such as intravenous chemotherapy and focal consolidative therapy—combination treatment with therapies such as laser photocoagulation, thermotherapy and brachytherapy—are being adopted in developed countries. The result is that some patients who once would have undergone enucleation can now be managed successfully without sacrificing visual outcomes or survival rates. Newer experimental treatments with localized delivery of chemotherapy are also offering hope that children can be spared the toxicities of intravenous

drugs or radiation (see “Retinoblastoma, Part One, Measured Enthusiasm for Intra-Arterial Therapy” in March’s *EyeNet*).

“The eye salvage rate has been increased by the introduction of new methods of treatment, such as systemic chemotherapy and focal consolidative therapy,” said Joan M. O’ Brien, MD, director of the Scheie Eye Institute and chairwoman of ophthalmology at the University of Pennsylvania in Philadelphia. “Secondary tumor risk has also been decreased due to avoidance of radiation, once the primary treatment for retinoblastoma. Radiation is associated with significant secondary tumor risk, and chemotherapy is thought to have lower secondary tumor risk.” The development of an international staging system specifically for retinoblastoma has also helped retina specialists and oncologists more accurately diagnose and treat patients.

Dr. O’Brien and colleagues recently opened a phase 1 study for treating retinoblastoma with carboplatin in a fibrin sealant delivered by subconjunctival injection.

Bleak outlook in developing countries. The picture for children with retinoblastoma in developing countries is far different. Where specialist care and technology are limited, 92 percent of children with retinoblastoma have less than a 20 percent chance of survival, according to the Daisy’s Eye Cancer Fund, an international non-governmental organization formed to battle retinoblastoma in the develop-

Cancer on the Run



Regression of macular retinoblastoma in the right eye of a 3-year-old patient of Dr. Stout’s.

ing world. The fund has begun a pilot initiative in Kenya working to bring effective sustainable local health care to children with retinoblastoma. “People in England, Canada and Kenya are collaborating and meeting every year for three days to talk about building a model for education, awareness, access to care and improved treatment,” said the fund’s medical director Brenda L. Gallie, MD. Dr. Gallie is also professor of molecular and medical genetics at the University of Toronto and senior scientist at the Ontario Cancer Institute of Princess Margaret Hospital.

Dr. Gallie noted that in countries such as Kenya, retinoblastoma is often identified late in the course of the disease; medical professionals are often ill-equipped to handle this cancer; and

access to specialists is difficult. “It’s exciting to know that by facilitating access we could make a real impact on mortality from this disease,” she said.

Hereditary vs. Not

Outcomes for children everywhere are also dependent on what form of the disease they have. Children with the hereditary form—meaning they have a germline mutation in RB1, the retinoblastoma tumor-suppressor gene—have a worse prognosis for cancer control and survival than those with the so-called sporadic, or nonhereditary, form of the disease.

Children with the hereditary form often present with bilateral disease and multiple tumors in both eyes; nonhereditary disease usually presents as one mass in one eye.

Cautiously good prognosis. Not surprisingly, hereditary retinoblastoma is a more complex disease, although outcomes for these children can be very good. “Often it’s recognized early—within the first month of life—because we frequently know if there’s a family history of the disease. We watch these children vigilantly, and if we see a tumor that starts to grow we treat it very aggressively,” said J. Timothy Stout, MD, PhD, professor of ophthalmology at Oregon Health & Science University in Portland. Treatment modality is based on the extent of the disease, the age of the child and the time of diagnosis, he said.

Neoplasm alert! Unfortunately, children with heritable retinoblastoma are also at increased risk for other neoplastic diseases. Although mutations in the RB1 gene were first associated with retinoblastoma, it’s now known to be associated with other cancers as well. So these children are at risk for osteosarcomas and pineal tumors in childhood and, as they move into adulthood, for breast cancer and cutaneous melanoma, according to Matthew W. Wilson, MD, professor of ophthalmology and director of the ocular oncology services at the Hamilton Eye Institute and St. Jude Children’s Research Hospital in Memphis.

Children with heritable disease who

are treated with radiation are at even greater risk for secondary cancers, Dr. Wilson said.

Genetic counseling. Because of the serious pathologies associated with RB1 mutations, most families with an incidence of retinoblastoma undergo genetic counseling and often genetic testing, according to Dr. Stout. Survivors of retinoblastoma are urged to have their children screened for both the mutation and the disease. Children of parents with the RB1 mutation have a nearly 50 percent chance of inheriting the mutation, and those who carry the mutation have a 90 percent chance of developing retinoblastoma, he said.

Following Kids After Treatment

Although the risk for a second retinoblastoma decreases significantly after 5 years of age, follow-up on all children posttreatment is critical, and particularly for those who carry the RB1 mutation. Retinoblastoma survivors are at increased risk for retinal detachment and cataracts in later life because of the retinal changes caused by the cancer and its treatment, Dr. Stout said. He recommends that treated children be followed closely until age 5 and at least yearly after that. Follow-up care should come from either a specialist in retinoblastoma or an ophthalmologist or pediatrician who feels comfortable with the disease, working in concert with an oncologist who can screen the child for secondary cancers.

Monitor after the etoposide or radiation. Of special note are a few cases of secondary acute myelogenous leukemia that have been reported from treatment with etoposide, one of the standard agents in three-drug retinoblastoma regimens. And although the general risk for secondary cancers associated with intravenous chemotherapies is not established, it’s thought to be lower than the risk from radiation, according to Dr. Wilson. “We’re still relatively early into the chemotherapeutic era—it’s only been widely used for 20 years—so the long-term significance of giving systemic chemotherapy to children with retinoblastoma is not yet fully known,” he said.

Why Mode of Treatment Matters Enucleation is still often indicated for retinoblastoma. There is, understandably, resistance to enucleation on the part of many families, but refusing enucleation can lead to overtreatment with other therapies. “People just do not want to see their children’s eyes removed, so in some situations we may end up treating an eye more than we should because the parents want everything done,” said Shizuo Mukai, MD, a surgeon at the Massachusetts Eye and Ear Infirmary and an assistant professor of ophthalmology at Harvard Medical School. “Certainly that makes sense if it’s the only eye remaining. But sometimes we do a lot for one eye when the other eye is perfectly fine, and saving the affected eye may contribute very little to the visual function of the child. The child may have already lost visual function due to the cancer.”

Losing a window but saving a soul. Dr. Mukai recalled a case of a child who had a very advanced tumor in one eye and the treatment of choice was enucleation. However, the parents were opposed to removal of the eye because their religious tradition instructed that a child losing an eye was the same as losing the soul. “The father was going to put the child up for adoption if we did the enucleation,” he said. “So we got social workers involved to show the family what the cosmetic results would be. And we finally got the parents on board to do the surgery. Fortunately, the cosmetic results were fantastic and the child and the family did very well afterward.”

1 Lin, P. and J. M. O’Brien. *Am J Ophthalmol* 2009;148:192–198.

None of the physicians interviewed for this story report related financial interests.

Info for Families

The University of Pennsylvania sponsors this patient-friendly site: www.oncolink.org. Type *retinoblastoma* in the search field.