

ONCOLOGY

Retinoblastoma, Part One: Measured Enthusiasm for Intra-Arterial Therapy

BY BARBARA BOUGHTON, CONTRIBUTING WRITER

Four years ago, a team at Memorial Sloan-Kettering Cancer Center and New York Presbyterian Hospital pioneered a technique for delivering localized chemotherapy through the ophthalmic artery in children with retinoblastoma. Their phase 1/2 study results were reported in 2008.¹ Nine children who had advanced retinoblastoma (Reese-Ellsworth V eyes) and who were slated for enucleation experienced dramatic regression of their tumors without severe systemic side effects or toxicity to the cornea, anterior segment or motility.

Qualms raised. While acknowledging that the results of the trial were impressive, some ophthalmic oncologists were concerned about the long-term effects of this treatment. In a previous article in *EyeNet* (February 2009) Carol L. Shields, MD, cautioned that the potential exists for vascular spasms with ischemic events, such as stroke, toxicity to the eye and brain, and fibrosis of the artery. Dr. Shields is professor of ophthalmology at Thomas Jefferson University and associate director of the ocular oncology service at Wills Eye Hospital in Philadelphia. And because the procedure uses fluoroscopy to visualize the catheter placement, there was concern about radiation exposure, including secondary cancers that might show up years later, particularly in children who have already been pretreated with radiation or chemotherapy, according to James J. Augsburger, MD, professor and chair-

man of ophthalmology at the University of Cincinnati and director of the ocular oncology service at the University's Academic Health Center.

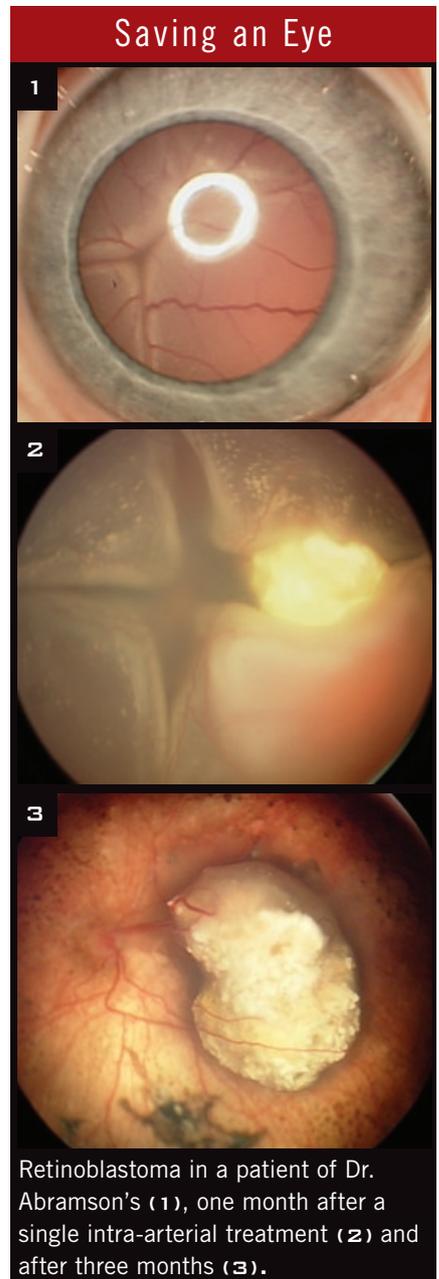
A number of medical centers in the United States and throughout the world have by now tried the technique, and its potential benefits and risks are clearer. Many ophthalmologists are excited about the treatment's potential to replace enucleation.

An Idea Is Born

The notion of localizing chemotherapy directly to the eye originated in Japan 15 years ago. In Japanese culture, there is grave opposition to the removal of patients' eyes, even if it will cure cancer. In some cases, parents will choose to leave the eye in place even if their child is expected to develop metastatic disease.

The Japanese technique infused melphalan into the carotid artery, before which a balloon catheter was passed into the artery and inflated to occlude it above the origin of the ophthalmic artery. The balloon catheter allowed the medication to perfuse the eye without reaching the brain.

While Japanese researchers documented excellent outcomes and low rates of complications with their technique, they also treated their patients with other therapies, such as hyperthermia and external beam radiation. So researchers elsewhere were slow to adopt the new idea because it was difficult to assess independently the contribution of the carotid infusion



Retinoblastoma in a patient of Dr. Abramson's (1), one month after a single intra-arterial treatment (2) and after three months (3).

on outcomes, according to David H. Abramson, MD, chief of the ophthalmic oncology service at Memorial Sloan-Kettering Cancer Center and professor of ophthalmology at Weill Cornell Medical College. Dr. Abramson and four colleagues—neuroradiologist Pierre Gobin, MD, pediatric oncologist Ira Dunkel, MD, and ophthalmologists Brian P. Marr, MD, and Scott E. Brodie, MD, PhD—later became the first team worldwide to try administration directly to the ophthalmic artery—not stopping at the carotid artery—and they have since performed it more than 270 times.

Success speaks. In Dr. Abramson's experience, all children with retinoblastoma who receive the ophthalmic artery treatment as first-line therapy experience significant regression, if not resolution, of their tumors, and 90 percent of these eyes have been salvaged. "For us, it has ended systemic chemotherapy for almost all children and ended 90 percent of enucleations we used to do," he said. In New York, the eyes of two-thirds of those patients who had progressed despite maximal therapy with all known modalities and who underwent the treatment as a salvage therapy have been saved. "That's not as high as 90 percent, but these are eyes where the alternative was nothing but enucleation. So it's really a spectacular story," Dr. Abramson said. Yet those children who had received maximal therapy and failed are also more likely to suffer side effects, primarily radiation retinopathy. "We think it is a result of all the treatments they have received in total," Dr. Abramson said. A small but significant fraction, 10 to 20 percent, of his patients who have undergone the ophthalmic artery technique experience dramatically improved vision as a result of the treatment, primarily because of resolution of retinal detachment, he added.

Drs. Shields noted, however, that systemic chemotherapy could also result in the same dramatic improvement in vision.

Some toxicities. While there have been no reports of serious side effects, some children (usually those in whom

it is used as a salvage treatment) have developed radiation retinopathy, and there has been one report of a hemorrhage inside the eye. And Dr. Shields said that others have seen retinal vascular sclerosis with ischemia.

Which drugs to use? The New York team initially used melphalan as their agent of choice because the Japanese had demonstrated its efficacy. (It has not been used intravenously against the disease.) While the concentration of melphalan given via the ophthalmic artery is high, the total dose to the rest of the body is low—which helps to cure the cancer but spares the child serious bone marrow toxicity, Dr. Abramson said.

The New York team has since tried other chemotherapeutic agents, including carboplatin, topotecan and methotrexate. In addition to using these drugs intra-arterially as single agents, the group has treated eyes with two drugs at the same session—often combining melphalan and topotecan. "The reason is that these two drugs are well known to have a synergistic effect in cancer," Dr. Abramson said. They are also trying digoxin because their research indicates that this drug and other cardenolides are toxic to retinoblastoma cells. While the number of treatment sessions for the initial group of nine children ranged from two to six, most children who undergo the treatment in New York can now be successfully treated in three sessions, three or four weeks apart, Dr. Abramson said. His team has also tried the technique in patients with bilateral retinoblastoma, with good initial outcomes. "We now call the technique 'chemosurgery' to emphasize the surgical precision and planning necessary to get good results," he said. "Long term, the treatment continues to be very successful," Dr. Abramson said. "These children are not dying, losing their eyes or suffering systemic side effects."

Concurring, With Reservations

While noting that the ophthalmic artery technique is promising, other ophthalmologists have been a bit more circumspect in their assessment. "It's

a very good tool for children who have tumor in one eye, and for those who have recurrence of tumor after they have failed other treatments," said Aparna Ramasubramanian, MD, a fellow at the ocular oncology service at Wills Eye Hospital. "But case selection is extremely important." In their experience with ophthalmic artery technique, Drs. Shields and Ramasubramanian and the team at Wills have seen good outcomes even in advanced tumors confined to the eye, they said, and complete regression of tumors in most cases.² In a review of 70 patients, there was a need for external beam radiotherapy in one child and enucleation in two children. The advantage of the treatment is that unlike systemic chemotherapy, it is selective, and so has the potential for fewer toxicities, they said.

Bilateral caveat. However, they caution that it is still too early to be using the technique on children with bilateral retinoblastoma. The reason is that these children usually carry a mutation in the RB1 gene that also predisposes them to pineal region tumors in the brain. "Our group believes that systemic chemotherapy can protect children with bilateral retinoblastoma from these brain tumors and so systemic chemotherapy would be beneficial for patients who have tumors in both eyes," Dr. Ramasubramanian said. However, children with bilateral retinoblastoma who failed systemic chemotherapy treatment might be candidates for the ophthalmic artery technique in the future, she added.

Radiation danger? The clinicians at Wills were initially concerned about the radiation effects of fluoroscopy delivered during the ophthalmic artery procedure, but a study they conducted indicated that the radiation exposure for each procedure is small, said Drs. Shields and Ramasubramanian. However, they cautioned, the cumulative radiation could predispose the children to develop cataracts later in life in the eye that received treatment.

Doubts about salvage potential. Other ophthalmic oncologists still urge a cautious approach until more

experience has been obtained. Dr. Augsburger has used the technique, with melphalan, as salvage therapy in five patients who had failed other therapies.

“It does produce a definite objective regression of the tumor. However, we have not found it to be very successful in the setting of salvage therapy for advanced disease,” he said. “In all five cases we treated, despite the initial promising result, the tumors recurred. I do not think that the future of this treatment will be as a salvage therapy after all other things have been done. It is more likely that it will be useful as an initial treatment.”

Dr. Augsburger generally urges a cautious approach until more knowledge has been gained regarding potential risks, such as hemorrhage or stroke in the eye, and induction of cancers years down the line from radiation exposure. “There are many advantages of this treatment over multiple doses of whole body chemotherapy. And it may be as effective or even more effective than whole body chemotherapy in eradicating the retinoblastoma. But consider that many of the problems with radiation therapy, which we started using in the 1920s, were not recognized until the 1970s or ’80s. And it took at least 10 years to get a handle on all the problems associated with chemotherapy regimens. So I think it’s too early to comment on what the actual impact of this treatment will be on these children.”

Promising does not equal perfect.

Dr. Abramson agrees that it is true that it takes years to truly know and understand the long-term side effects of therapies. In fact, one of the reasons the New York group wanted to convert from systemic chemotherapy was precisely because of the significant side effects now being seen from this modality years after its introduction for the treatment of retinoblastoma. Among these side effects are deaths from chemotherapy itself, permanent hearing loss and secondary leukemias, according to Dr. Abramson. There are also concerns (though no data on retinoblastoma patients) that the

systemic chemotherapy may lead to infertility or sterility in the reproductive years. In addition, the need for ports, transfusions and hospitalizations for fever/neutropenia takes a toll on the children and their families and significantly adds to the cost of care. “The tiny dose of melphalan used for intra-arterial chemosurgery does not cause any of these side effects, but we will monitor all our cases for any ocular or systemic side effects for a long time,” Dr. Abramson said.

Enthusiasm Wins the Day

Dr. Abramson and others remain fans of the ophthalmic artery technique. “It’s so clearly superior as a treatment,” said Dr. Abramson. “It’s less toxic, cheaper and faster. The only reason some centers are not doing it is that it’s a complicated treatment that requires a lot of coordination, including coordination among interventional neuroradiologists and ophthalmologists familiar with retinoblastoma. We now have the option even in advanced cancer cases of keeping the eye—an eye that looks normal, moves normally and allows the orbital tissues to grow normally. In some cases, these eyes can even get back sight.”

Just as satisfying, Dr. Abramson added, is the fact that this technique is now being used at Memorial Sloan-Kettering and New York Presbyterian Hospital for other neoplasms, including the first uses for brain and brain stem tumors. “It is a tribute to ophthalmic oncology that we may have opened a window of opportunity for neurosurgeons for possible management of cancers of the brain.”

1 Abramson, D. H. et al. *Ophthalmology* 2008;115:1398–1404.

2 Shields, C. L. et al. *Retina* 2009;29(8):1207–1209.

None of the physicians interviewed report related financial interests.

Next Month: Part Two will discuss the prognosis and incidence of secondary cancers for teenagers and young adults who were treated in infancy or childhood.

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