Benefits and Risks of Intraarterial Chemotherapy for Retinoblastoma: An Update

Positive results with the technique have been replicated at numerous centers worldwide.

BY DAVID H. ABRAMSON, MD, FACS

Last year in *Retina Today's* November/December issue focusing on ocular oncology, I recapped the evolution of therapy for retinoblastoma over the past century, up to the development and early experience with intraarterial chemotherapy. In that article, I said, "Experience to date suggests that superselective ophthalmic artery chemotherapy is more effective, faster, better, and safer than conventional treatments for this cancer, which already had good success rates."

This year, as this issue on ocular oncology is being assembled, I am freshly returned from the biennial International Society of Ocular Oncology meeting in Buenos Aires, Argentina (November 14-17, 2011), where my New York collaborators and I presented our experience at a symposium on intraarterial chemotherapy. With this perspective, I can report that it now seems the entire world of ocular oncology has embraced this approach. Intraarterial chemotherapy for retinoblastoma has been performed in 31 countries, including Iran, Syria, and South Africa, and in multiple centers in the United States. Perhaps the best proof of success is the ability of other centers to replicate our results. In Buenos Aires, presenters from the United States, including Timothy G. Murray, MD, MBA, FACS, and Carol L. Shields, MD, spoke enthusiastically about the procedure and its results, and reports from clinicians in England, Italy, and other countries were also very favorable.

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At Memorial Sloan-Kettering Cancer Center in New York, where the technique was pioneered, we have now passed our 500th infusion of intraarterial chemotherapy for retinoblastoma. At our institution this technique has replaced systemic chemotherapy and radiation as primary therapy for retinoblastoma; we have not used systemic chemotherapy or radiation as primary management for retinoblastoma in any child over the age of 3 months since we began using the intraarterial approach 5.5 years ago.

In the November 2011 issue of *Archives of Ophthalmology*, which is dedicated to the theme of retinoblastoma, there are 3 editorials on the subject of intraarterial chemotherapy for retinoblastoma—including 1 by this author—and several clinical and laboratory reports on the procedure.

So although intraarterial chemotherapy is a relatively

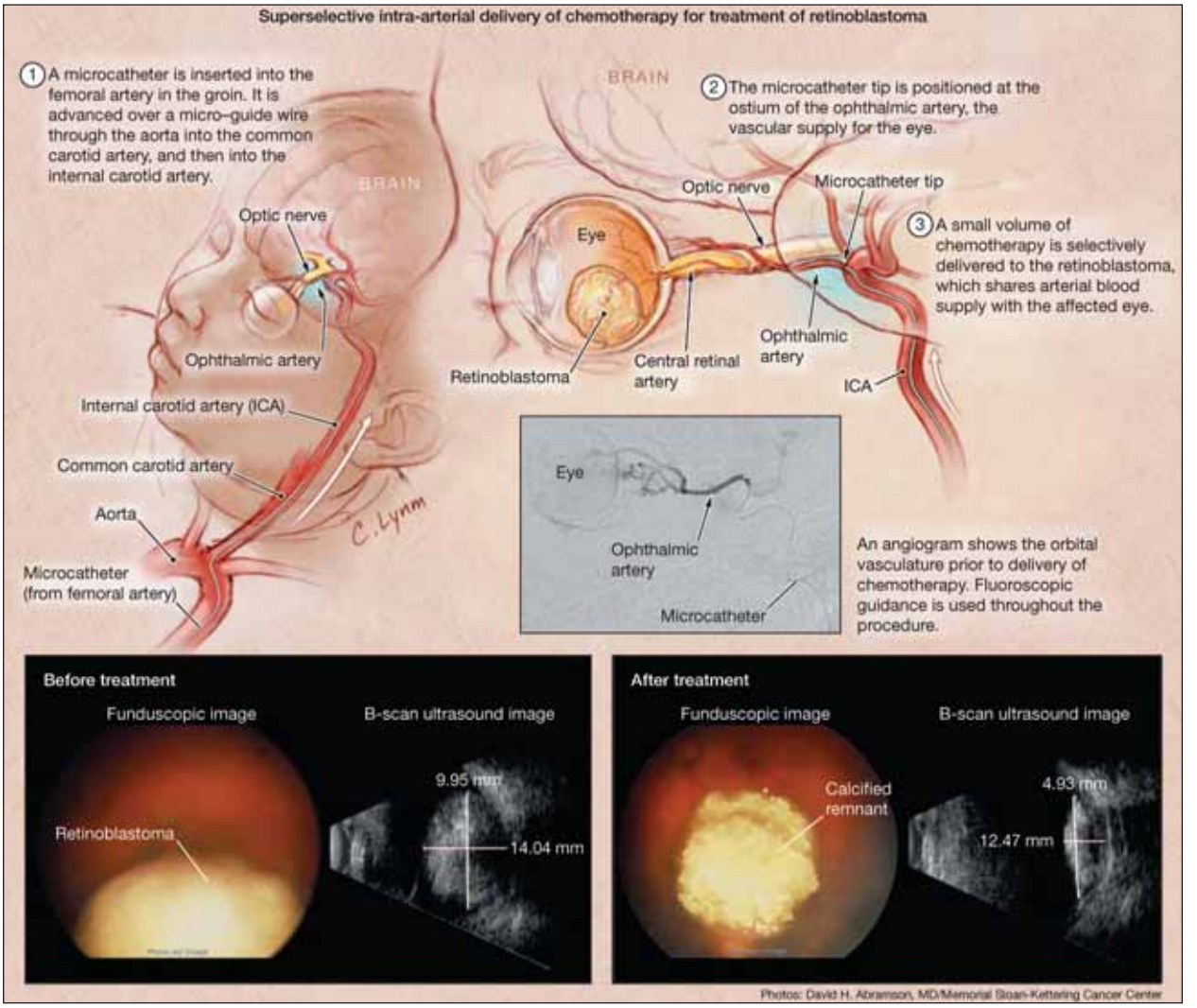

Figure 1. A novel approach to treating a rare childhood malignancy, retinoblastoma, is superselective ophthalmic artery infusion of chemotherapy, which delivers a chemotherapeutic agent directly to the eye while minimizing systemic exposure. It is proving to be a simple and superior technique that not only destroys tumors but also can preserve and even restore vision in some cases.

young procedure—the first treatment was performed at our institution less than 6 years ago—there is tremendous interest in it, and our experience has been replicated by numerous centers all over the world.

This article briefly updates what we now know about intraarterial chemotherapy and looks forward to what may be coming in the near future.

4-YEAR EXPERIENCE

Earlier this year we reported the 4-year experience with intraarterial chemotherapy at Memorial Sloan-Kettering Cancer Center.[1] In 95 eyes of 78 patients with unilateral or bilateral retinoblastoma, the Kaplan-Meier estimates of ocular event-free survival rates were 70% for all eyes, 82% for eyes that received intraarterial chemotherapy as primary treatment, and 58% for eyes that had previous treatment failure with systemic chemotherapy and/or external beam radiation therapy (Figure 1). This is especially noteworthy because most of these were advanced or very advanced eyes scheduled for enucleation. Fully 90% of the eyes we previously enucleated can be treated with intrarterial chemotherapy. Reports from other centers that are soon to appear in print not only replicate these results, but some report even better ocular survival rates. In most cases, the chemotherapeutic agent was melphalan, with or without topotecan, and dosage was determined by age and blood vessel anatomy. Catheterization was successful in 98.5% of procedures,

and 289 chemotherapy injections were performed. There were no significant extraocular complications, no deaths or strokes from the procedure, and there was no need for overnight hospitalization.

All children in this series are alive. Two who developed metastatic disease were treated with intravenous chemotherapy and local radiotherapy and are doing well. In our experience, which has been replicated by others, there is no significant short- or long-term systemic toxicity from intraarterial chemotherapy. Neutropenia was seen after 11.4% of treatment sessions in 18 patients, but no child in our series required a blood transfusion.

We have also performed this therapy bilaterally in patients with bilateral disease.[2] This procedure, which we call tandem therapy, seems to be safe for the patient and the eye even in advanced disease. Tandem procedures require caution because of the "double dose" of chemotherapy. When we do tandem treatments we use different agents in each eye to minimize systemic exposure of chemotherapeutic drugs. No significant systemic adverse events were seen in our small series reported last year. In those 4 patients, aged 5 to 19 months, electroretinograms (ERGs) showed visual improvement in half of the eyes for which pretreatment ERGs were available.

JAPANESE EXPERIENCE

A form of selective ophthalmic arterial chemotherapy injection for retinoblastoma using a balloon catheter has been practiced since the 1980s in Japan, and investigators there recently reported long-term prognosis in a series of 408 eyes of 343 patients.[3] While our procedure differs from theirs in important ways—the indications for treatment, the method of catheterization, and the drug dosage—it is encouraging to note that, in 1452 procedures, these investigators achieved a success rate of 98.8% with few severe adverse events, more than half of eyes treated with the balloon technique were preserved, and more than half of eyes without macular tumors maintained a visual acuity of greater than 20/40. Twelve secondary cancers occurred in 11 patients, with a cumulative incidence of 1.3% at 5 years, 4.8% at 10 years, and 5.8% at 15 years. Thus the incidence of second cancers was not increased with this procedure over the 25-year period studied in Japan. Of patients in this series, which was begun 1986, only 6 have died.

SAFETY AND COMPLICATIONS

It is important to note that intraarterial chemotherapy is a surgical procedure. That is why we prefer to call it "chemosurgery." As with any surgery, therefore, it requires developing a plan, assembling a competent team, choosing the right anesthesia, and knowing how to handle complications. It is a dynamic procedure; as in any surgery, the surgeon must make decisions and adapt to changes on the spot.

Complications have been reported from several centers, including a recent report of vascular obstructions in 2 eyes in a retrospective series of 38 catheterizations in 17 eyes.[4] It is worthwhile to note that these complications occurred early in the experience with intraarterial chemotherapy at the reporting institution. It may also be of interest that the first author of that report, Carol Shields, MD, spoke enthusiastically of the intraarterial procedure in her presentation at the symposium in Argentina and said complications are rarely encountered now that the team at Wills Eye Hospital has more experience with it.

Although the adoption of a new technique invariably brings new complications, it is also true that complications associated with the older technique are left behind when that procedure is abandoned. We no longer see the transfusions, infected ports, fevers, and neutropenia associated with systemic chemotherapy. We also avoid the ototoxicity and hearing loss that are associated with systemic carboplatin chemotherapy.[5]

WHERE ARE WE NOW?

What are the implications of the experience with intraarterial chemotherapy reported to date by our center and an increasing number of other centers around the world? First, it seems clear that this procedure achieves better results in retinoblastoma than any other treatment option for eyes with advanced disease, extensive seeding (both subretinal and vitreous), and extensive retinal detachment. In treatment-naïve eyes, approximately one-third of children in our experience have needed only one infusion of intraarterial chemotherapy—no laser, no cryotherapy, no radiation. And this experience has been replicated at other centers.

The recognition that a single chemotherapy treatment alone can cure a solid cancer is remarkable in the cancer world. There are few solid cancers that can be cured with chemotherapy alone. We have calculated that the dose the eye receives in intraarterial administration of chemotherapy is about 100 to 1000 times the dose delivered by conventional intravenous chemotherapy. That apparently makes the difference between achieving a response that is followed by recurrence vs achieving a response that is durable, that cures the cancer.

For eyes that previously received conventional treatment, the only treatment alternative until now has been enucleation. Intraarterial chemotherapy is now saving about 70% of these eyes long-term, defined as 2-year

Kaplan-Meier survival.[1] This is remarkable for eyes that previously would have been universally enucleated. Our lowest success rate—around 50%—is seen in eyes that have progressed despite both external beam irradiation and systemic chemotherapy. However, these eyes have all come to enucleation in the past, so a 50% salvage rate represents a major step for our field and our patients.

The reasons for enucleation in our hands and those of others are mostly straightforward: progressive disease and vitreous seeds. Vitreous seeds remain the biggest challenge in retinoblastoma. The prognosis with conventional systemic chemotherapy and radiation in these cases is poor, with perhaps one-third of eyes saved. In our experience with intraarterial chemotherapy, in the overwhelming majority of these cases the children are keeping their eyes, keeping their lives, keeping whatever vision they had when they came to us, and in some cases seeing vision improved; in approximately 75-77% of cases, ERGs have remained steady or improved.

In conventional management of retinoblastoma, eyes with total retinal detachment have been considered to have very poor prognosis and are usually enucleated. They are designated as class E eyes (for "enucleation") in the International Classification of Retinoblastoma scheme.[6] We have found that we can save more than 90% of these eyes, that in about a third of cases the ERG shows significant improvement, and in about 10% of cases with flat ERG before treatment there is some usable vision afterward. We speculate that the reason for the extraordinary results in these poor prognosis eyes is that the chemotherapy agent collects in the subretinal fluid and the eye itself acts as a depot, providing added efficacy.

As noted above, most complications that have been reported with intraarterial chemotherapy are related to technique, which would be expected. The technique is new and challenging, and there will be a learning curve even for experienced clinicians. With 5 years' experience, we have observed that no 2 children have the same anatomy of blood vessels in the orbit; the vascular anatomy is different in every human we have seen so far. Therefore, one cannot read an anatomy book and be prepared to perform this procedure. We have not seen 1 patient whose anatomy corresponds to the description in Gray's Anatomy.

Incidentally, intraarterial chemotherapy is less expensive than conventional treatment of retinoblastoma. We were the first to do this analysis, and now 2 other centers worldwide have confirmed that it is true in their hospitals as well. About two-thirds of the expense in cancer treatment, especially in children, comes from treating the complications of cancer treatment: the transfusions, the infected ports, the fever, the neutropenia, the secondary infections. All of this consumes time and money and has its own set of complications. With the intraarterial approach we avoid all of those costs.

The drugs we are currently using are melphalan, topotecan, and carboplatin. We have done 2000 ERGs to measure the toxicity of these drugs, and are preparing papers on this subject. We still have a lot to learn regarding which drugs are the most effective and in exactly what doses and combinations. We know that the doses we are using are safe systemically and almost always completely safe locally, despite reports of localized hemorrhages or Roth-like spots. Choroidal infarctions caused by cotton contamination, which have been reported by other centers, can be devastating but are avoidable.

Our hope in the future, however, is not to have to use any of those drugs. We are actively looking for nonchemotherapy drugs, which we believe in the future will replace chemotherapy and avoid the associated toxicity.

We look forward to the continued development of intraarterial chemotherapy. This approach has now been used to treat other tumors, including unresectable brain tumors, although this application is in its infancy. We continue to read with interest the reports from other centers of their experience with intraarterial chemotherapy, including reports of complications, as we value any experience that can help us to improve the technique.

I am sure we will continue to learn more about intraarterial chemotherapy—the good and the bad—as we all get more experience and longer follow-up. I am also sure that this technique is here to stay and will end the use of systemic chemotherapy and radiation, and I hope this revolutionary technique is just another step in the progression of improving treatment for retinoblastoma. ■

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