Chemosurgery for Retinoblastoma

What We Know After 5 Years

SUPERSELECTIVE OPHTHALMIC ARTERY DELIVERY of chemotherapy for retinoblastoma (“chemosurgery”) was initially performed just 5 years ago in an institutional review board–approved experimental protocol (for advanced eyes scheduled for enucleation) and was first reported in 2008. It has now been performed in 26 countries worldwide (Argentina, Australia, Brazil, Canada, China, Colombia, the Czech Republic, Egypt, France, Germany, Great Britain, Holland, India, Iran, Israel, Italy, Jordan, Korea, Pakistan, Russia, Slovakia, Spain, Switzerland, Thailand, Turkey, and the United States) and has subsequently been featured in a number of articles in the non–peer-reviewed literature, including stories in JAMA and the New York Times. Although some centers have almost completely abandoned primary radiation and/or systemic chemotherapy as a result of their experience with chemosurgery and claim a dramatic reduction in the need for enucleation, other centers have declined to perform the procedure. Concern has been raised about the absence of long-term data, about full knowledge of toxicity, and about other adverse issues. What do we really know about this approach?

As of June 22, 2011, there have been 20 publications on chemosurgery in peer-reviewed journals. At least 10 additional papers are in press or are under review. What do the published papers say?

ABILITY TO DO THE TECHNIQUE

All centers are using the same protocol that we introduced for treatment. In our first report, cannulation was successful in 9 of the 10 children. Recently, we reported that, in nearly 300 attempts, catheterization succeeded in 98.5% of cases. In Miami, successful cannulation was achieved in 100% of cases (26 procedures), and in Philadelphia, catheterization was successful in 37 of 38 cases. Thirteen successful catheterizations were reported from Switzerland.

DRUGS AND DOES USED

In New York, we have reported on the use of melphalan (3-7.5 mg [first suggested by the Japanese]), topotecan hydrochloride (0.3-0.4 mg), carboplatin (15-30 mg), methotrexate sodium, and digoxin. In Miami, all patients received melphalan. Eyes were initially treated with 3 or 5 mg of the drug used, but because of inadequate responses, all children now receive 7.5 mg. In Philadelphia, all patients received 3 mg of melphalan, and 6 of 17 patients also received concurrent carboplatin (30 mg). In Switzerland, melphalan alone was used.

There may never be a “standard” dose for treatment. Eye size, vascular anatomy (large vessels to the lacrimal artery, supratrochlear artery, and middle meningeal artery), wedge flow, clinical response and prior exposure to chemotherapy (depleting marrow reserves), carboplatin allergy, untoward reaction to previous therapy, and, of course, clinical response will dictate the doses chosen, and clinicians must recognize that, like surgery, this is a dynamic decision that often needs to be made in real time. However, the importance of these dose adjustments in reducing toxicity while optimizing efficacy remains to be sorted out.

CLINICAL RESPONSE

The recent report of our 4-year experience emphasized that there was a statistically different success rate between eyes that were treated de novo (“naive”) and eyes that underwent prior, conventional therapy that failed. Overall, 70% of eyes were salvaged at 2 years, 81.7% of eyes initially treated with chemosurgery at 2 years were salvaged, and 58.4% of eyes that underwent prior conventional management that failed were salvaged at 2 years. These were mostly very advanced eyes that would have been enucleated, and 83 of the 95 eyes were Reese-Ellsworth group V eyes (73 group Vb eyes and 10 group Va eyes). Both eyes could be treated in the same session (“tandem therapy”).

Eyes from Miami also had advanced intraocular disease. All tumors treated were Reese-Ellsworth group Vb eyes (and International Classification D). When 3 or 5 mg of melphalan was used on these eyes, 36% of them were enucleated, but when 7.5 mg was used, no eye came to enucleation. Overall 76% of eyes were spared enucleation. In Switzerland, all 13 patients were felt to be “candidates for enucleation,” and all but 1 of the tumors were classified as “D.” Enucleation and external beam irradiation were avoided in all cases.

Of 12 eyes managed with primary chemosurgery in Philadelphia, 8 (67%) were salvaged. Eyes classified as “C” or “D” had 100% globe salvage. Of 4 eyes treated after conventional treatments failed, 2 (50%) were saved. To salvage 81% to 100% of eyes (most candidates for enucleation) is unprecedented. To salvage 50% to 58% of eyes after conventional treatment failed (where the only
alternative was enucleation) represents a major advance for the field.

SYSTEMIC COMPLICATIONS

All centers have reported on their systemic complications. To date, no deaths or strokes have been reported. To our knowledge, no patient has (yet) been reported to have a second cancer, but it is well known that patients with germinal retinoblastoma are at significant risk for the development of a second cancer, even if no external beam radiation or chemotherapy is given. Because almost all of the eyes that have been treated with chemosurgery are very advanced and because it is the very advanced eyes that are predisposed to metastasis, it is expected that some patients with retinoblastoma treated with chemosurgery will die. We have reported 2 cases of metastasis. Both patients are presently in remission.

Bronchospasm and decreased tidal volume during the procedure have been noted and reported by most groups; the frequency of these events seems to be related to the depth of anesthesia during the procedure. We reported iodine dye allergies and 1 transient occlusion of the superficial femoral artery. Hyperemia in the distribution of the large supratrochlear artery has been noted in 15% of cases. Neutropenia is often noted but is usually minimal and reached grade 3 or 4 in only 11.4% of our cases (mostly when the total dose of melphalan exceeds 0.4 mg/kg). No patient in any series has required a port. To our knowledge, there has been only 1 patient in the literature who developed fever/neutropenia (and that child previously had 6 months of chemotherapy).

VISUAL FUNCTION

We have reported on visual function before and after treatment by measuring visual acuity, pupillary responses, and electroretinographic responses to photopic and scotopic testing. Overall, 70% of eyes have shown the same electroretinographic responses before and after treatment, 20% have shown a more than 25-µV improvement in 30-Hz flicker responses, and 10% have shown worsening responses. Of the eyes with retinal detachment at the time of treatment, 30% have shown an improvement in electroretinographic function of more than 25 µV. We (and others) now have a few children who are older and have Snellen fractions of 20/20 after treatment. However, the majority of our children are very young, and so precise visual acuity measurements are challenging.

Only one other center (in Switzerland) has reported on visual results. Of 13 eyes treated in this center, half of the evaluable eyes had visual acuity of better than 20/100, and 2 had visual acuity of 20/32. This center felt that the treatment had no adverse effect on vision in any child.

OCULAR ADVERSE EFFECTS

We initially reported periorcular edema, transient hyperemia in the distribution of the supratrochlear artery in 15% of cases, epiphora, and temporary ciliary loss; this was confirmed in the Philadelphia report that also noted orbital congestion limiting ocular motility. All of these cases appeared to be transient.

Recently, intraocular adverse effects have also been reported. Only one of these reports is associated with visual acuity or electroretinographic testing to know the visual impact of the reported findings. In some cases, the eyes had previously had extensive treatment (including systemic chemotherapy, laser therapy, and cryotherapy), rhegmatogenous and nonrhegmatogenous retinal detachments, and surgery for retinal detachment, so it is difficult to know whether the adverse effects are due to tumor effects, retinal detachment, prior treatment (including retinal detachment surgery), drug effects, or wedge flow (which causes rapid alterations in the pressure and flow within the perfused vessel, resulting in hemorrhages) or to combinations of these many features.

We first reported on vascular occlusion in 1 eye. From Miami, 1 eye was reported to have transient scattered intraretinal hemorrhages and peripapillary cotton wool spots, and in 4 cases (15% of total treatments), delayed vitreous hemorrhage led to enucleation. From Switzerland, 2 of 13 eyes (15%) had “sectoral choroidal atrophy,” and 1 of these 2 eyes also had retinal emboli. Vision was not affected, and the hemorrhages resolved. From Philadelphia, 3 cases of “ophthalmic artery stenosis,” 2 cases of central or partial vein occlusion, and 9 cases of “subtle retinal pigment epithelial mottling . . . that slowly evolve to later-onset underlying choroidal atrophy” were reported.

One report has raised the question of whether the radiation exposure during the procedures will possibly cause second cancers or cataracts. A recent report on the long-term follow-up of the Japanese cohort (using selective [not superselective] infusion), however, revealed no increase in either.

Within 5 years of performing the first procedure, chemosurgery has been successfully performed in 26 countries worldwide and reported in 20 peer-reviewed articles. No cases of stroke, death, a need for a port, or significant systemic adverse effects have yet developed. Most children required 3 outpatient treatments (range, 1-8 treatments). There has been no need for transfusion of any blood product, and both naive eyes and advanced eyes scheduled for enucleation have been salvaged in 81% to 100% of cases worldwide. Fifty percent of eyes that underwent conventional retinoblastoma treatment that failed (and in which the only alternative was enucleation) have been salvaged. Vision has been retained or improved in 90% of cases, but the eyes were often limited by a preexisting macula tumor and a prior extensive retinal detachment.

Despite the fact that systemic chemotherapy alone rarely (if ever) cures solid tumors in children and despite the fact that systemic chemotherapy alone rarely cures intraocular retinoblastoma, one-third of the eyes treated with chemosurgery are cured with chemotherapy alone. It represents one of the very few cancers that can be controlled with single-agent chemotherapy alone.

David H. Abramson, MD
Author Affiliation: Ophthalmic Oncology Service, Memorial Sloan-Kettering Cancer Center, New York, New York.

Correspondence: Dr Abramson, Ophthalmic Oncology Service, Memorial Sloan-Kettering Cancer Center, 70 E 66th St, New York, NY 10021 (abramsod@mskcc.org).

Financial Disclosure: None reported.

REFERENCES