

Advances in Chemotherapy for Retinoblastoma

Super-selective intraarterial infusion has proved successful with few complications.

REVIEWED BY DAVID H. ABRAMSON, MD, FACS

Note: There are no chemotherapies approved for use in children by the US Food and Drug Administration, so all chemotherapy for children should be considered off-label.

The following article is based on material presented by Dr. Abramson at Yale Retina 2009: New Frontiers in Retina Diagnosis and Therapy; April 3, 2009; New York City.

Dr. Abramson would like to acknowledge the work of his collaborators, including Pierre Gobin, MD, Interventional Neuroradiologist at New York Presbyterian Hospital; Ira Dunkel, MD, Pediatric Oncologist at Memorial Sloan-Kettering Cancer Center (MSKCC); Scott Brodie, MD, PhD, with MSKCC and Mount Sinai School of Medicine, who performed all the electrophysiological testing for patients treated with this technique; and Brian Marr, MD, Ophthalmic Oncologist at MSKCC.

More than 100 years ago, external beam irradiation was shown to be effective for retinoblastoma;¹ it took more than 50 years, however, to optimize the dose, fractionation, the energy and portals, and also to recognize the importance of avoiding the anterior segment. Ultimately, radiation has become the most common treatment for retinoblastoma (after enucleation), and retinoblastoma is one of the few cancers that can be cured by radiation alone.

Despite the success of radiation for retinoblastoma, a disturbing consequence of treatment in genetic cases is the development of secondary nonocular cancers, of which there are numerous types associated with the retinoblastoma gene.^{2,3} More than 95% of children in the United States with retinoblastoma survive;⁴ however, these secondary nonocular cancers occur in retinoblastoma at a rate of approximately 0.5% to 1.0% per year throughout life,⁵ and the mortality for these cancers is approximately 50%.⁶ Although the retinoblastoma gene

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causes these second cancers without radiation exposure, these secondary nonocular cancers develop sooner and more often in the head in irradiated children.⁵ Thus, a worldwide search was undertaken to find an alternative approach that does not employ external beam radiation for the treatment of intraocular retinoblastoma.

SYSTEMIC CHEMOTHERAPY FOR RETINOBLASTOMA

Since the mid-1990s, systemic chemotherapy has been an accepted treatment for intraocular retinoblastoma, often producing a dramatic reduction in tumor size.⁷

Despite worldwide success in reducing tumor size with chemotherapy, a considerable amount of disenchantment exists with this approach because of the side effects of systemic therapy, which are physical, psychological, and emotional in nature, as described by Wilson et al.⁸ That study followed 25 consecutive retinoblastoma patients treated at St. Jude Hospital in Memphis, TN. These patients collectively underwent 895 outpatient appointments, 698 examinations under anesthesia, 230 focal treatments, 1,272 anesthetics, and traveled 822,312 miles for treatment. In addition, although systemic chemotherapy significantly reduces the size of ocular tumors, the treatment rarely qualifies as a cure. The majority of retinoblastoma tumors for which systemic chemotherapy is used tend to grow back after the

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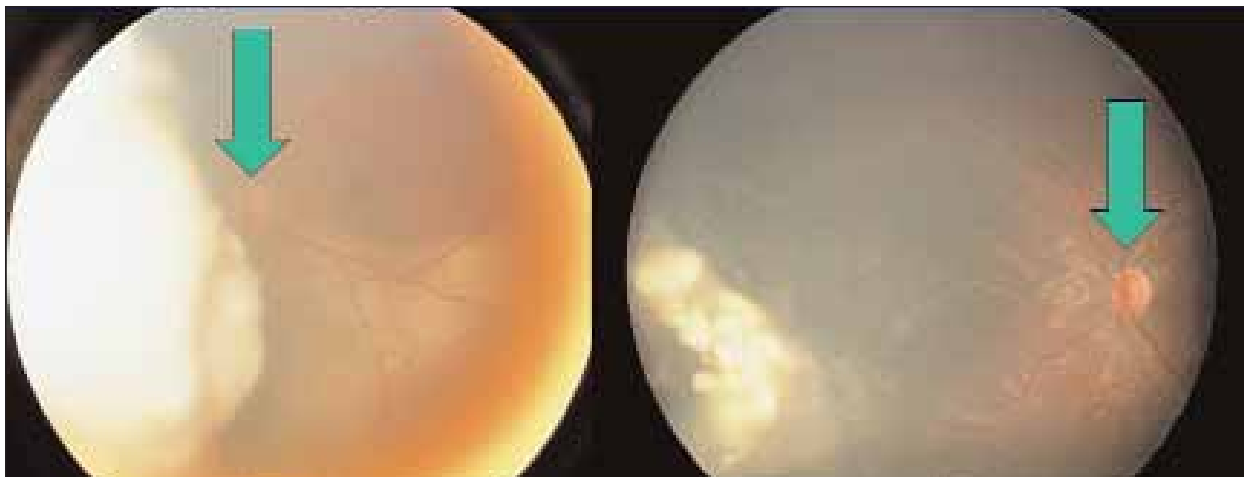


Figure 1. Eye with retinoblastoma for which intraarterial melphalan was used. The photo on the left (A) is the eye before treatment. The optic nerve is noted with the arrow. The photo on the right (B) is the same eye after three treatments with intraarterial melphalan.

chemotherapy is discontinued unless additional treatment techniques are employed.^{9,10} Similarly, few solid cancers can be cured by chemotherapy alone.

SIDE EFFECTS OF SYSTEMIC CHEMOTHERAPY

As stated above, one of the reasons alternative treatments to external beam radiation were sought was the incidence of secondary cancers. For more than 10 years, we have known that systemic chemotherapy for retinoblastoma is associated with secondary cancers.¹¹ Meadows et al¹² reported that the major established cause of acute myelocytic leukemia is chemotherapy and that between 2% and 12% of patients treated with epipodophyllotoxins develop secondary leukemia.

There is a difference, however, between radiation- and systemic chemotherapy-induced cancer. Radiation-induced secondary cancer, on average, takes many (5-70) years to develop, but chemotherapy-induced cancer can occur after the initial injection of chemotherapeutic drugs for retinoblastoma. There have been cases in which patients being treated for retinoblastoma with chemotherapy have not even completed the treatment course because they have developed and succumbed to secondary leukemia. Recently, Dan Gombos, MD, published a case series on 15 patients who developed secondary acute myelogenous leukemia after being treated with chemotherapy for retinoblastoma.¹³ Since that report was published, additional cases have occurred.

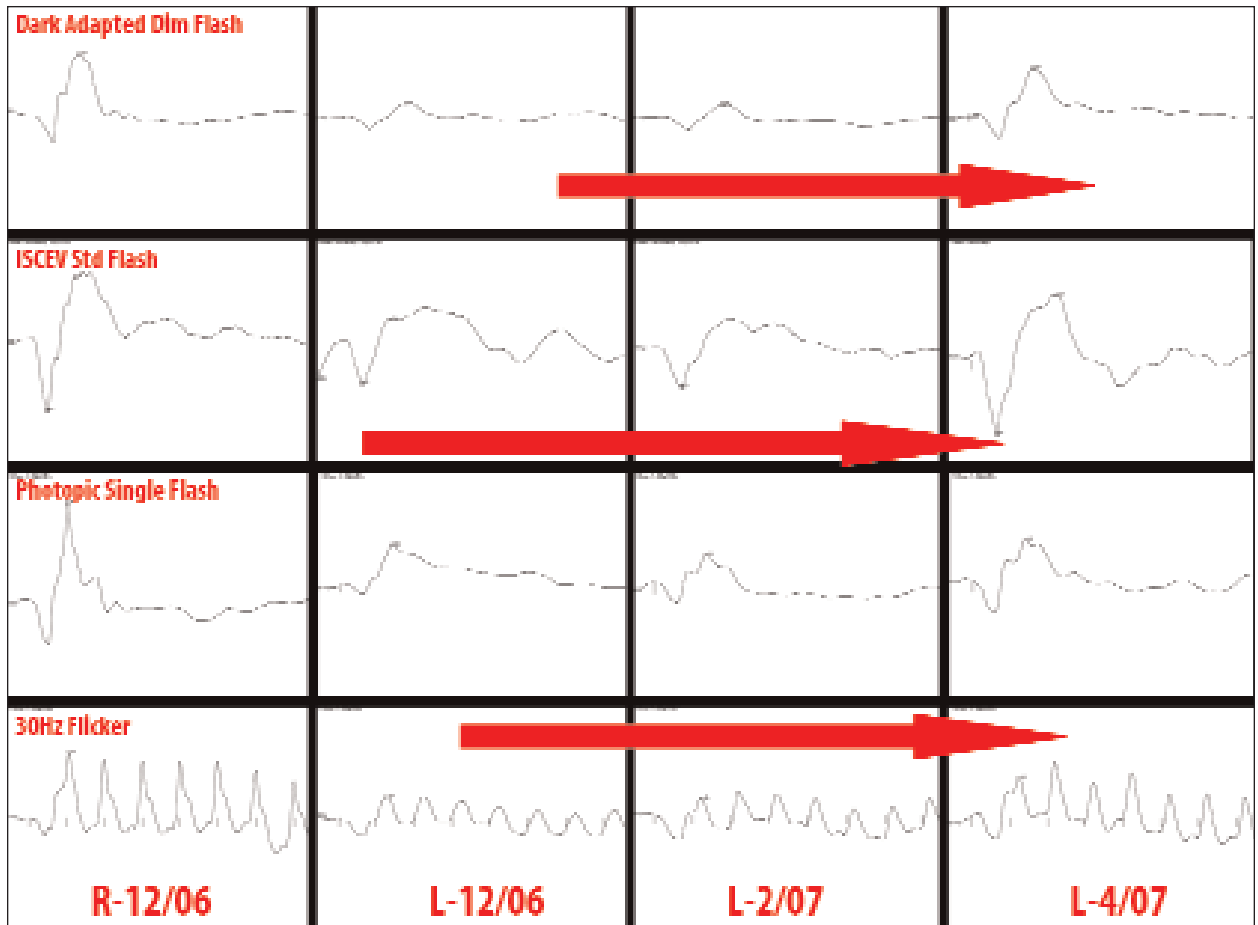
Chantada et al¹⁴ noted a worldwide trend of patients with retinoblastoma who are being referred to pediatric oncologists rather than an ophthalmologist for the management of retinoblastoma because of the use of systemic chemotherapy.

Chan et al¹⁵ performed a study showing that in eyes where salvage external beam radiation was used in addition to systemic chemotherapy, the intraocular complication rate is higher. The salvage therapy was shown to be successful in preserving useful vision in patients, and no deaths or second cancers were reported.

Another side effect of systemic chemotherapy that has been documented is hearing loss. The most commonly used chemotherapeutic drug in combination with other agents is platinum-based carboplatin (Paraplatin, Bristol-Myers Squibb), which has become preferred over cisplatin, also platinum-based. One of the common side

TABLE 1. INTRAVENOUS CHEMOTHERAPY COMPLICATIONS

Port	100%
RBC Transfusion	100%
Platelet/Transfusion	50%
Febrile Neutropenia	50%
Hospitalization	100%
Infertility	Unknown rate, but possible higher risk with IV than IA



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Figure 2. ERG recordings with multiple techniques from the patient in Figure 1. Responses from the right eye (first column) are normal. Responses from the left eye (columns 2-4) show improvement in retinal potentials over a 4-month period.

effects with these agents is ototoxicity, which causes progressive hearing loss that in some cases leads to complete deafness.¹⁶ Reports are now emerging that this side effect with carboplatin has been underreported and that permanent hearing loss may affect 5% of patients on the drug, based on retrospective review.¹⁷

Infertility is another side effect of systemic therapy. Long-term data regarding chemotherapy's effect on fertility for postpubertal children show that there is a distinct sterilizing effect of chemotherapy. A recent article in the *New England Journal of Medicine* cited a definitive negative effect of chemotherapy on the fertility of prepubertal girls and boys.¹⁸ The authors state that the elimination of alkylating agents, such as carboplatin or etoposide, is a necessary goal of cancer treatment in children to reduce the toxicity and risk of infertility.

My colleagues and I reviewed the world literature on complications from chemotherapy; 100% of children treated for retinoblastoma require ports, 100% undergo at least red blood cell transfusions, and many have

decreased platelets or platelet transfusions.¹⁹ Approximately 50% of these children have febrile neutropenia, and 100% of them are ultimately hospitalized with complications from treatment (Table 1).

PERIPHERAL COMPLICATIONS

Blood transfusions themselves place an enormous burden on pediatric patients and their families in terms of cost, time, and anxiety. Additionally, bacterial contamination in transfusions occurs in approximately one in 1,000 to one in 3,000 cases. Blood is mislabeled one in 14,000 cases, the incidence of hepatitis B is one in 205,000 cases, and in both hepatitis C and HIV the incidence is one in 2 million cases. Transfusion-related acute lung injury occurs in about one in 5,000 cases, but the mortality rate of this complication is 5% to 10%. Blood transfusions also carry the risk for transmission of Creutzfeldt-Jacob, Chagas, malaria, and Lyme diseases. The rates of Babesiosis, a malaria-like parasitic disease, in endemic areas (eg, New York State) fall between one in 600 and

TABLE 2. INTRAARTERIAL CHEMOSURGERY COMPLICATIONS

Port	0%
RBC Transfusion	0%
Platelet/Transfusion	0%
Febrile Neutropenia	one patient x 1
Hospitalization	one patient x 1
Infertility	Unknown but likely lower rate than IV

one in 800 cases. This disease, although rare, is serious and can be fatal in 5% to 10% of cases.

SUPER-SELECTIVE INTRAARTERIAL INFUSION

Clearly, systemic chemotherapy works well for the tumor but not well for the patient; thus, we began evaluating a new technique, super-selective ophthalmic artery infusion of chemotherapy for retinoblastoma. The concept of this method is to deliver a high concentration of drug to the cancer and achieve less exposure via a low dose systemically to the patient. The goal is to eliminate the need for enucleation and systemic chemotherapy in children with retinoblastoma.

The procedure, performed under general anesthesia, is accomplished via a single femoral artery stick with a 1.4-mm 4-French catheter and then a 450- μ m micro-catheter, which is passed up through the femoral artery into the abdominal and thoracic aorta, to the internal carotid arteries, and into the ophthalmic artery. The ophthalmic artery of the children (some of whom were as young as 3 months old) we treated in the first year measured between approximately 550 μ m and 1000 μ m.

For the chemosurgery procedure, we administer 2 mg to 7 mg of melphalan, an alkylating agent (Alkeran, GlaxoSmithKline) diluted in a 30-cc solution and injected over 30 minutes. The procedure is performed an average of three times only, once every 3 weeks. It is known that about 10% of the carotid blood flow passes through the ophthalmic artery, and from that less than 1% of the carotid blood flow actually reaches the eye.²⁰ The ocular vasculature is varied in pattern, and, because of this, the treatment is not as evenly distributed in some cases. When the majority of the drug is deposited in the largest

TABLE 3. COSTS OF CANCER TREATMENT: SYSTEMIC CHEMOTHERAPY VS INTRAARTERIAL CHEMOSURGERY*

Systemic Chemotherapy	Intraarterial Chemosurgery
↓	↓
Per cycle: \$4,453**	Per cycle: \$17,393
Overall: \$158,105	Overall: \$80,479
* Table 3 information appears courtesy of Amanda Kosack, Memorial Sloan-Kettering Cancer Center.	
**More money is spent on complications than actual treatment.	

blood vessel, the supratrochlear, localized redness and madarosis may occur. One way that we have found to avoid this is to occlude the supratrochlear artery at the time of the procedure.

We have also found that it is important to pulse the injections because the laminar blood flow in the ophthalmic artery results in inconsistent and even retrograde flow with a continuous injection.

The goal of intraarterial infusion is to eliminate the need for enucleation and systemic chemotherapy in children with retinoblastoma.

Figure 1 shows an eye with retinoblastoma for which intraarterial melphalan was used. The photo on the left (A) is the eye before treatment. The optic nerve is noted with the arrow. The photo on the right (B) is the same eye after three treatments with intraarterial melphalan. Figure 2 shows the electroretinograph recordings from the patient in Figure 1. Responses from both eyes are shown using multiple techniques (photopic and scotopic). The responses from the right eye are normal. Improvement in the potentials from the left eye within approximately 4 months is clear.

SUMMARY

As of March 1, 2009, we have performed more than 150 successful infusions using this technique to replace systemic chemotherapy for patients with retinoblastoma. In our experience, we have had good success in eradicating the cancer with very few ocular complications and no significant systemic complications (Table 2).

Further, the average cost for treating patients for sys-

temic chemotherapy at Memorial Sloan-Kettering Cancer Center is \$158,000, one-third of which is spent treating the cancer itself, and the other two-thirds of which is spent on treating the complications from the treatment. Intraarterial treatment is half the cost of IV administration (Table 3).

In summary, we have found that intraarterial infusion is faster, more effective, safer, and cheaper than systemic chemotherapy for retinoblastoma. This new approach, in my opinion, represents the future for treating children with retinoblastoma. ■

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