Retinoblastoma 2012

BY AMY C. SCHEFLER, MD

Retinoblastoma is a rare disease. There are only an estimated 250 to 350 cases per year in the United States, and the disease accounts for only 4% of pediatric malignancies. Nonetheless, clinical and basic scientific observations about this disease continue to advance each year, and 2012 was no exception. This brief paper reviews recent clinical developments in the field.

INTRAARTERIAL CHEMOTHERAPY

Many publications in 2012 from the United States and Europe centered on an increased understanding of the dosing, complications, side effects, and outcomes of the intraarterial chemotherapy approach. This treatment was initiated in Japan more than 20 years ago.[1] In 2008, Abramson et al[2] published the first report in the United States about the use of this treatment with modern catheterization techniques.

Three studies this year by Venturi et al,[3] Shields et al,[4] and Abramson et al[5] examined Kaplan-Meier rates of ocular salvage in groups of untreated and previously treated patients (Table 1). Two of the three groups[4,5] reported that ocular salvage rates in eyes that were naïve to treatment were higher than in those that had previously undergone systemic chemotherapy or other treatments. In contrast, Venturi et al[3] reported that eyes that had previously undergone other forms of treatment responded better to intraarterial chemotherapy than treatment-naïve eyes. Overall, salvage rates of eyes in both groups of patients in all centers was above 50% at 2 years.

Figure 1. Fundus photo of a left eye with Reese-Ellsworth Group Vb/International Classification Stage D retinoblastoma.

As with all new therapies, several authors have raised concerns about potential new complications that were

TABLE 1. LARGE SERIES OF INTRAARTERIAL CHEMOTHERAPY FOR RETINOBLASTOMA PUBLISHED THIS YEAR

Authors	No. Eyes/ No. Patients	Ocular Salvage Rate: Naïve Eyes	Ocular Salvage Rate: Previously Treated Eyes
Abramson et al[5]	76/67	80% at 2 years (Kaplan-Meier)	50% at 2 years (Kaplan-Meier)
Venturi et al[3]	38/41	45.6% at 2 years (Kaplan-Meier)	95.5% at 2 years (Kaplan-Meier)
Shields et al[4]	17/17	67%	50%
Muen et al[13]	15/14	N/A	80%
Schuaiquevich et al[14]	8/8	87% at 12 months (by Kaplan-Meier)	N/A
N/A=data not available in publication			

TABLE 2. REPORTED COMPLICATIONS OF INTRAARTERIAL CHEMOTHERAPY

Authors	Complication
Muen et al[13] Shields et al[4] Venturi et al[3]	Choroidal/retinal infarct
Muen et al[13] Shields et al[4]	Rhegmatogenous or tractional retinal detachment
Muen et al[13] Shields et al[4]	Vitreous hemorrhage
Muen et al[13] Venturi et al[3]	Third cranial nerve palsy
Muen et al[13] Venturi et al[3] Abramson et al[5]	Hyperemia of skin in supratrochlear distribution
Muen et al[13] Venturi et al[3] Schaiquevich et al[14] Shields et al[4]	Orbital congestion limiting motility
Muen et al[13] Venturi et al[3] Shields et al[4] Abramson et al[5]	Bronchospasm during procedure
Venturi et al[3] Shields et al[4] Abramson et al[5]	Loss of lashes
Venturi et al[3] Abramson et al[5]	Grade 3 or 4 neutropenia

A series of intraocular and orbital side effects and complications have been noted [with intraarterial chemotherapy], many of which are transient, some of which are permanent and/or vision-limiting.

not an issue with older therapies (Table 2).[6-9] There have been no intracranial cerebrovascular events and no deaths reported after the procedure in any centers. A series of intraocular and orbital side effects and complications have been noted, many of which are transient, some of which are permanent and/or vision-limiting. The most common transient complications after the procedure seem to be orbital congestion limiting motility, loss of lashes, and a skin rash along the supratrochlear distribution. The most common vision-limiting side effects seem to be retinal and choroidal infarcts.

Several authors have noted that, as with all surgical procedures, there appears to be a learning curve with the procedure in which the interventional neurosurgeon becomes more facile with the procedure over time and fewer intraocular complications occur, especially ischemic ones.[7] A close examination of Table 2 reveals that groups with larger series (eg, more experience) have lower complication rates than those from centers reporting their first small series of patients.

TABLE 3. INTRAVITREAL CHEMOTHERAPY FOR RETINOBLASTOMA STUDIES PUBLISHED 2011-2012

Authors	No. Injections/ Eyes/Patients	Drug(s) and Technique Used	Prior Treatment	Ocular Salvage Rate
Munier et al[15]	135/30/30	Melphalan (124); carboplatin (2); or ranibizumab (9); AC paracentesis; 32-gauge needle; cryotherapy	SC, IAC, EBR; focal therapy; brachytherapy	25/30 (83%)
Kivela et al[16]	131/6/6	Methotrexate; AC paracentesis; 30-gauge needle	SC	5/6 (83%)
Ghassemi and Shields[17]	33/12/12	Melphalan; 30-gauge needle through peripheral cornea/iris root or pars plana; cryotherapy	SC, EBR	4/12 (33%)
Smith et al[18]	2/2/2	Carboplatin; 32-gauge needle; subconjunctival injection of carboplatin	SC	0/2 (0%)

SC=systemic chemotherapy
IAC=intraarterial chemotherapy
EBR=external beam radiotherapy
AC=anterior chamber

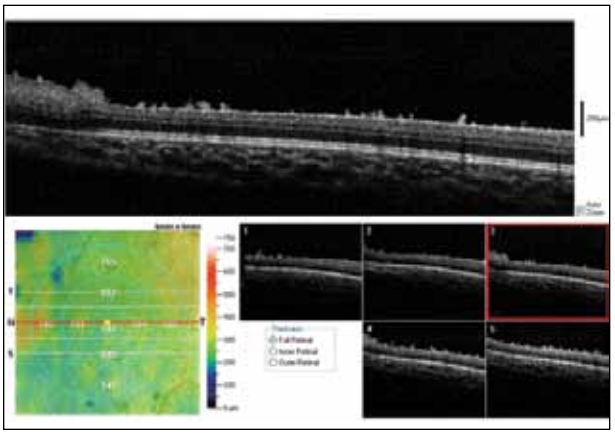

Figure 2. OCT demonstrating retinoblastoma tumor arising from within the retina as well as vitreous seeds that have settled on top of the inner retinal surface.

INTRAVITREAL CHEMOTHERAPY

Although the intravitreal injection has become widely adopted as routine practice for adult retinal diseases, it has not taken hold as a treatment approach for retinoblastoma, despite the fact that vitreous seeds represent the major cause of tumor control failures requiring enucleation surgery (Figures 1 and 2). The injection of chemotherapy intravitreally was first reported by Ericson and Rosengren[11] in 1961 using thiotepa for the treatment of retinoblastoma[10] and has been studied extensively in animals. It is widely performed in retinoblastoma patients in Japan. Recently, at the biennial meeting of the International Society of Ocular Oncology in Buenos Aires, in November 2011, Suzuki and Kaneko reported that they had performed 896 injections in 237 eyes of 227 patients and that only 1 eye (0.4%) was judged to have had extraocular extension caused by an injection at a mean follow-up of 91 months. Of note, many of these patients also had treatment with intraarterial chemotherapy or radiation.

Nonetheless, for years, clinicians taking care of retinoblastoma patients in the United States and Europe were concerned about the use of intravitreal injections due to the risk of extraocular spread of tumor outside the globe. Karcioglu et al[12] published the results of a pathology study in 1985 that convinced clinicians for several decades that biopsies were risky. In this study, the authors performed 16 biopsies in 4 globes (3 with retinoblastoma and 1 with uveal melanoma) using a 25-gauge needle. Approximately half of the needle tracks demonstrated viable tumor cells on sectioning, although the authors reported that there were fewer cells than had been demonstrated to cause metastases in animal models.

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Over the past year, several authors have reported on the emerging use of this treatment in a renewed interest in salvaging eyes with resistant vitreous seeds and a belief that perhaps the risk for extraocular extension may not be as great as previously thought (Table 3). Of note, there was a wide range of ocular salvage rates with this technique, from 0% to 83%, with salvage rates increasing with series size.

CONCLUSION

Rapid innovation in clinical approaches to treatment continues in retinoblastoma despite the rare nature of the disease and minimal collaboration among centers. Intraarterial and intravitreal chemotherapy both show promise for improved ocular salvage and visual results, although very long-term follow-up has not yet been achieved in patients treated with these approaches. ■

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