Successful salvage intravenous chemotherapy after tandem selective ophthalmic artery infusion chemotherapy in bilateral retinoblastoma

Hyun J Kim, Maura Di Nicola, James J Augsburger, Basil K Williams Jr

We report the case of a 9-month-old girl with bilateral retinoblastoma who had incomplete tumor resolution after selective ophthalmic artery infusion chemotherapy (SOAIC). Systemic chemotherapy, rarely used as salvage therapy after SOAIC, with systemic carboplatin, etoposide, and vincristine achieved complete and sustained regression in both eyes.

Key words: Intraarterial chemotherapy, retinoblastoma, selective ophthalmic artery infusion chemotherapy

The introduction of selective ophthalmic artery infusion chemotherapy (SOAIC) for the treatment of retinoblastoma has increased globe salvage rates compared to intravenous chemotherapy, particularly in advanced cases.[1-3] Eyes that have failed SOAIC frequently undergo enucleation and less commonly external beam radiation therapy (EBRT).[4] Due to the increased risk of second primary malignancies associated with the administration of EBRT and the inherent functional and cosmetic implications of enucleation, salvage systemic chemotherapy is a reasonable approach. Herein, we describe a patient with bilateral retinoblastoma who successfully responded to systemic chemotherapy with local consolidation after the initial failure of SOAIC.

Case Report

A 9-month-old girl was referred for evaluation of bilateral, intraocular white tumors that were noted during evaluation for strabismus by a pediatric ophthalmologist. Past family, medical, and ocular histories were unremarkable. Anterior segment examination was normal in both eyes. Fundus examination of the right eye disclosed a white retinal tumor centered on the macula extending to the optic disc, surrounded by shallow subretinal fluid containing a few small subretinal

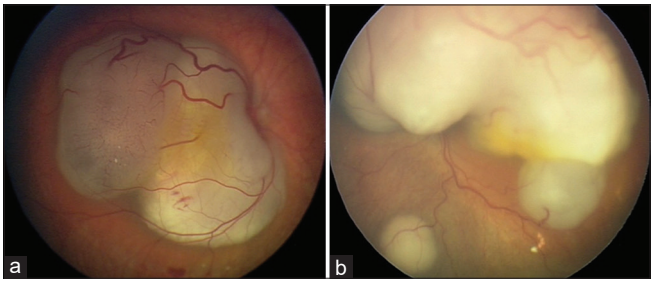

Figure 1: (a) Color photograph of the right eye at presentation demonstrating a large retinal mass abutting but not completely obscuring the optic disc. There is a small cuff of subretinal fluid with few localized subretinal seeds inferior to the main lesion. (b) Color photograph of the left eye at presentation demonstrating three distinct retinal tumors, the largest of which completely obscures visualization of the optic disc

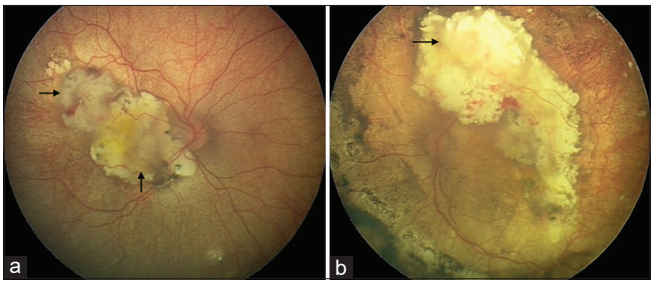

Figure 2: After eight cycles of selective ophthalmic artery infusion chemotherapy and two rounds of transpupillary thermotherapy in each eye, the right eye (a) showed considerable consolidation with two areas concerning for persistent tumor (arrows). (b) The left eye also showed significant regression with complete visualization of the optic disc, but an area of fluffy residua (arrow) was still present

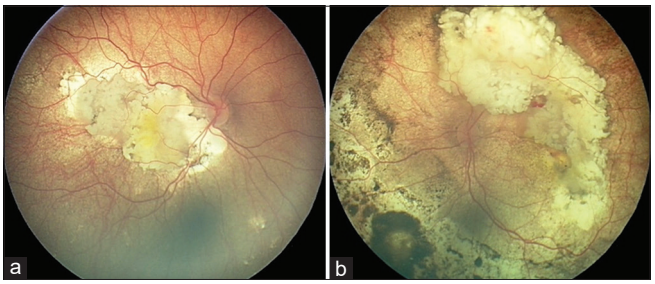

Figure 3: Four cycles of systemic chemotherapy with vincristine, etoposide, and carboplatin were administered as salvage therapy, and complete resolution was achieved in both the right (a) and left (b) eyes

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Ocular Oncology Service, Department of Ophthalmology, University of Cincinnati College of Medicine, Cincinnati, OH, USA

Correspondence to: Dr. Basil K Williams Jr, Ocular Oncology Service, University of Cincinnati College of Medicine, 231 Albert Sabin Way, Suite 5414, Cincinnati, OH 45267-0527, USA. E-mail: basilkwilliams@gmail.com

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seeds [Fig. 1a]. Fundus examination of the left eye showed three discrete white retinal tumors, the largest of which involved the entire macula and prevented visualization of the optic disc [Fig. 1b]. The tumor complex was surrounded by subretinal fluid that contained numerous subretinal seeds. Magnetic resonance imaging of the orbits and brain confirmed bilateral enhancing intraocular masses consistent with retinoblastoma, without evidence of retrobulbar or intracranial extension. Based on the International Intraocular Retinoblastoma Classification (IIRC), the patient was diagnosed with group C disease in the right eye and group D disease in the left eye.

After discussion of potential benefits and risks of currently available management options with the patient's family, bilateral SOAIC was chosen as initial treatment. Monthly tandem SOAIC was initiated with single-agent melphalan at a dose of 6 mg. After the first two cycles, both eyes showed partial regression of all retinal tumors and subretinal seeds with complete resolution of secondary serous retinal detachment. However, examination after the third round of SOAIC showed no further shrinkage of still viable-appearing retinal tumors. The melphalan dose was increased to 8 mg and carboplatin (60 mg) and topotecan (0.6 mg) were added to the regimen. Four more cycles of SOAIC, eight total, and two sessions of local consolidation in the form of transpupillary thermotherapy (TTT) were administered in both eyes. No evidence of systemic toxicity was appreciated clinically, and complete blood count revealed mild myelosuppression.

Despite treatment, calcific lesions with fleshy, residual areas of viable tumor were present in both eyes [Fig. 2], and intravenous chemotherapy with carboplatin (18.6 mg/kg), etoposide (5 mg/kg), and vincristine (0.05 mg/kg) was initiated as salvage therapy. Complete clinical regression was achieved in each eye following the third cycle of systemic chemotherapy [Fig. 3], and one additional cycle of systemic chemotherapy was administered for consolidation. The patient has remained in clinical remission 24 months after completion of intravenous chemotherapy, with rare episodes of emesis in the immediate post-treatment period and limited myelosuppression not significant enough to warrant a transfusion.

Discussion

Over the past decade, SOAIC has consistently demonstrated improved tumor control and globe salvage rates in patients with retinoblastoma.[1-3] Intravenous chemotherapy with adjuvant local treatment historically achieved globe salvage rates of 90% or better in groups A, B, and C, but much lower rates in group D (47%).[5] In group B and C eyes, SOAIC has demonstrated globe salvage rates similar to those of systemic chemotherapy, ranging from 95% to 100%.[3] The benefit of SOAIC over systemic chemotherapy as primary treatment was most pronounced in group D eyes where eye salvage rates of 85%–100% have been achieved.[4,6] This improved efficacy is presumed to be due to the superior ocular penetration of chemotherapy with SOAIC compared to intravenous administration.[7] Additional benefits of SOAIC include a reduced side effect profile consisting of dose-related incidence of neutropenia,[2] periocular erythema,[8] and rarely ophthalmic vascular events.[3] Side effects of intravenous chemotherapy include alopecia, ototoxicity, neutropenia, anemia, and thrombocytopenia, but are usually transient.[4]

There is debate on the optimal first-line therapy for advanced bilateral retinoblastoma.[1] Some institutions initiate treatment with systemic chemotherapy combined with local consolidation via laser or cryotherapy, while others prefer tandem SOAIC.[1,9] Given the potential increased eye salvage rates for SOAIC over intravenous chemotherapy (IVC) in group D eyes and in an attempt to reduce the systemic side effects of IVC, the family elected to proceed with SOAIC. Our patient demonstrated a rapid initial response to melphalan SOAIC monotherapy. When tumor regression stagnated, carboplatin and topotecan were added to the SOAIC regimen. However, after eight cycles of SOAIC and adjuvant TTT, persistent active tumor remained. Despite incomplete response to SOAIC, the tumors in both eyes demonstrated marked sensitivity to systemic carboplatin, etoposide, and topotecan.

Given intravenous chemotherapy must undergo first-pass metabolism and cross the blood-retinal barrier, only a small fraction of the administered medication is thought to reach the eye. While doses of carboplatin and topotecan administered in SOAIC are approximately one-third the dose used in systemic chemotherapy, a nontumor-bearing pig model revealed 100 times greater drug concentrations in the vitreous with SOAIC.[10] The success of systemic chemotherapy in this case could be due to the mechanistic difference of the chemotherapeutic agents administered intravenously. This tumor may have been more susceptible to a topoisomerase II inhibitor like etoposide compared to topotecan, which inhibits topoisomerase I. In addition, the inhibition of microtubule formation secondary to vincristine binding to tubulin or a combination of both these factors may have allowed for complete tumor resolution.

Conclusion

Retinoblastoma resistant to SOAIC is often treated with enucleation and less commonly EBRT due to an increased risk of second primary malignancies, especially in patients with germline mutations. Systemic chemotherapy is much less commonly utilized as salvage therapy. However, this case highlights the potential benefits of systemic chemotherapy after failure of tumor resolution with SOAIC.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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