Selective ophthalmic artery infusion of chemotherapy for advanced intraocular retinoblastoma: initial experience with 17 tumors

Clinical article

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Object. Retinoblastoma is the most common ocular neoplasm in children. Left untreated it spreads to the brain via the optic nerve. Traditional therapy is enucleation, and while this procedure is still the most common treatment worldwide, modern eye-preserving therapies can often spare the globe. However, patients with retinoblastoma often present in advanced stages of the disease when these globe-preserving strategies are often insufficient to prevent enucleation. In these challenging cases, direct infusion of chemotherapy into the ophthalmic artery has been attempted to achieve tumor control. The authors’ aim in this study was to report on their initial experience with and clinical results for this approach.

Methods. The authors prospectively collected data on all cases of retinoblastoma treated with selective intraophthalmic melphalan at Bascom Palmer Eye Institute. All cases were classified as International Intraocular Retinoblastoma Classification (IIRC) Group D or Reese-Ellsworth Group Vb, had not responded to aggressive multimodal therapy consisting of chemotherapy and focal consolidating laser therapy, and were pending enucleation. Using digital subtraction angiography, a microcatheter was navigated under roadmap guidance into the ophthalmic artery, and melphalan was infused over 40 minutes. Early in the series, patients were treated with 3 or 5 mg of melphalan, but after low response rates occurred all eyes were treated with 7.5 mg of melphalan. All patients were examined with funduscopy while under anesthesia 3 weeks after treatment and every 3 months thereafter. Patients with persistent disease were retreated with repeat infusions of melphalan.

Results. Twenty-six procedures were performed to treat 17 tumors in 15 patients. Successful cannulation of the ophthalmic artery was achieved in all cases. The follow-up ranged from 3 to 12 months, with a mean of 8.6 months. Overall, 76% of the tumors responded to therapy and these cases were spared enucleation. The average number of treatments was 1.5 per tumor. Of the responders, 54% responded to a single dose of melphalan. Treatment with the higher dose of 7.5 mg up front was associated with a lower enucleation rate (0% vs 36%) as compared with the lower starting dose. Delayed vitreous hemorrhage occurred after 4 (15%) of 26 treatments, and these cases were treated with enucleation.

Conclusions. In this challenging group of advanced retinoblastomas refractory to aggressive multimodal therapy, virtually 100% of eyes are generally enucleated. In contrast, the authors’ protocol of infusing melphalan directly into the ophthalmic artery led to a dramatic decrease in the enucleation rate to 23.5%. While it is now the treatment of choice for refractory retinoblastoma at their center, its role in less advanced disease remains to be elucidated.

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Key Words • retinoblastoma • selective ophthalmic artery infusion • chemotherapy infusion • melphalan

Abbreviations used in this paper: ICA = internal carotid artery; IIRC = International Intraocular Retinoblastoma Classification.

Rates. However, for advanced disease with vitreous seeding (Reese-Ellsworth Group Vb or IIRC Group D), even this aggressive multimodal therapy results in a high rate of treatment failure.14 In patients with refractory disease, enucleation rates approach 100% regardless of therapy.

In this cohort with advanced disease, selective intraarterial infusion of chemotherapeutic agents into the ophthalmic artery has been suggested in an attempt to limit the need for radiation therapy and exposure to chemotherapy and to lower enucleation rates. While a few reports have been published in the ophthalmological literature,1,15 no relevant cases have appeared in the
neurosurgical literature. As endovascular neurosurgeons continue to expand their technical repertoire, they may be called upon to perform this novel technique to treat this challenging disease. We report our experience with this technique as well as its clinical outcomes and complications.

Methods

Our study protocol was approved by the local ethics committee, and written informed consent was obtained for all patients. We prospectively collected data on all patients with retinoblastoma treated with selective intraophthalmic infusion of chemotherapy at our institution between 2008 and 2009. Clinical variables gathered included patient age, IIRC group, Reese-Ellsworth group, previous treatment, clinical response rates, complications, and rates of enucleation. A clinical response was defined as stable or decreased tumor size and lack of tumor vascularity according to funduscopic examination at the most recent follow-up visit.

Treatment Protocol

All patients with advanced retinoblastoma treated at the Bascom Palmer Eye Institute receive full consolidating systemic chemotherapy (carboplatin, vincristine, and etoposide) as well as a focal laser therapy. Patients with advanced (IIRC Group D) tumors demonstrating persistent activity despite this aggressive multimodal therapy are offered selective intraophthalmic melphalan as an alternative to enucleation. Melphalan was chosen after a study evaluating a number of chemotherapeutic agents revealed that retinoblastoma cells were most chemosensitive to melphalan. Unfortunately, systemic toxicity has limited melphalan’s role in treatment paradigms when the drug is administered intravenously, although it is an ideal candidate for local therapy.

Despite an early report describing a clinical response at an intraophthalmic dose of 3 mg of melphalan, we were unable to achieve tumor control at this dose, and patients initially treated at this low dose frequently required retreatment at a higher dose of 7.5 mg. Given this experience, we no longer start intraophthalmic melphalan therapy at this low dose. Instead, all patients are treated up front with 7.5 mg. Treatment doses higher than this were reported to result in side effects such as local edema and neutropenia. In 1 patient we offered up-front intraophthalmic melphalan as first-line therapy before aggressive multimodal therapy to limit exposure to prolonged systemic chemotherapy.

For patients with bilateral disease, both eyes were treated with intraophthalmic melphalan only if both eyes met the above criteria of advanced disease refractory to aggressive therapy. In those cases, the eye determined to have the greater disease burden was treated with 7.5 mg, and the other eye was treated with 5 mg. The maximal systemic dose of melphalan before reaching myelosuppression was calculated by multiplying the body surface area according to the Mosteller formula by 16/m². In all cases the maximum systemic dose calculated was < 15 mg.

Funduscopic examination while the patient was under anesthesia together with photography and ultrasonography was performed for all treated eyes 3 weeks after therapy and every 3 months thereafter. Tumors that demonstrated an increased size, persistent tumor vascularity, or persistent atypical tumor margin were retreated with intraophthalmic melphalan and focal consolidating laser therapy. Cases of retreated tumors that failed to respond to these treatments were enucleated.

Endovascular Technique

All procedures are performed while the patients are under general anesthesia. A 4 Fr vascular sheath is placed into the femoral artery. The vascular sheath and diagnostic catheter are perfused with heparinized saline throughout the procedure. A 4 Fr angled Terumo guide catheter is navigated over a 0.035-in guidewire into the cervical ICA where anteroposterior and lateral views of the intracranial circulation are obtained. Systemic heparinization is then administered to maintain the activated clotting times between 250 and 300 seconds. Under roadmap guidance, a Mirage wire and Marathon microcatheter (ev3 Neurovascular, Inc.) are navigated into the proximal ophthalmic artery. A selective ophthalmic artery angiogram is obtained. We do not advance the microcatheter more than a few millimeters from the ostium of the ophthalmic artery. Melphalan is then mixed with 10 ml of iodinated contrast diluted with 30 ml of sterile normal saline for a total volume of 40 ml. This solution is then pulse-injected over 30 minutes. Intermittent fluoroscopy under subtracted roadmap confirms continued placement of the microcatheter in the ophthalmic artery as well as selective infusion into the artery. When the infusion is complete, the microcatheter is removed and final anteroposterior and lateral angiograms of the intracranial circulation are obtained. The diagnostic catheter is removed from the sheath, and the sheath is removed under compression. Direct manual compression is then applied for 15 minutes.

Results

Clinical Characteristics

Between 2008 and 2009 we performed 26 intraophthalmic infusions of melphalan to treat 17 tumors in 15 patients. The patient ages ranged from 6 months to 8 years, with a mean age of 3.2 years. Of these 15 patients, 8 (53%) had bilateral disease. In 2 of these patients with bilateral disease, the tumors met the criteria for treatment with intraophthalmic melphalan. All tumors had evidence of vitreous seeding, and all but 1 had not responded to aggressive multimodal therapy. Follow-up ranged from 3 to 12 months, with a mean follow-up of 8.6 months. Patient characteristics are summarized in Table 1.

Technical Results

Successful ophthalmic cannulation was achieved in 100% of the 26 treatments, including 1 case with an aberrant origin of the ophthalmic artery from the ipsilateral middle meningeal artery. The mean fluoroscopy time was 13.7 minutes, and the mean contrast load was 23.6 ml.
Ophthalmic artery infusion of chemotherapy

Using the intermittent negative roadmapping technique, all infusions were visualized as intraophthalmic for the duration of the infusion.

**Tumor Control and Chemotherapy Dose**

Of the 17 tumors treated with intraophthalmic melphalan, 13 (76.5%) responded to treatment and were spared enucleation, resulting in an overall ocular preservation rate of 76.5% during the follow-up period. Of the responding lesions, 7 (53.8%) responded to a single dose of melphalan and 6 (46.2%) required 2 doses before responding. The number of treatment sessions ranged from 1 to 2, with a mean of 1.4 sessions. Overall, 4 (23.5%) of 17 tumors did not respond to therapy, and thus were treated with enucleation. Tumors treated with an initial dose of 7.5 mg were associated with lower enucleation rates (0%) as compared with those initially treated with a lower dose (36%), despite the fact that all of the tumors initially treated with the lower dose were retreated with a 7.5-mg dose. The mean follow-up period for lesions initially treated with this higher dose was 6.2 months (range 3–8 months). There were no tumor recurrences during the follow-up period.

**Illustrative Case**

A 7-year-old girl presented with an advanced IIRC Group D, Reese-Ellsworth Group Vb retinoblastoma (Fig. 1 upper). She was treated with systemic carboplatin, vincristine, and etoposide as well as focal consolidating therapy and repeated melphalan infusions. The patient remained disease-free after 1 year of follow-up.

**Treatment Complications**

Systemic complications occurred following 3 (11.5%) of 26 treatments. Two patients who were scheduled for repeat melphalan infusion experienced a delay due to neutropenia, and 1 patient was admitted for fever and discharged the next day after a negative workup. There were no cases of infection or sepsis, and there were no deaths.

There were no technical complications from the procedure such as vessel dissections, perforations, or thrombus formation. Neither were there any cases of stroke or brain damage. There was 1 groin hematoma that was self-limited.

**Ocular complications** occurred after 5 (19%) of 26 treatments. Four consisted of delayed vitreous hemorrhage discovered at the 3-week funduscopic examination. There were no signs or symptoms referable to the hemorrhage, and thus the exact time of hemorrhage is unknown. Patients in all 4 cases subsequently underwent enucleation. The fifth ocular complication consisted of ischemic symptoms following treatment with intraophthalmic melphalan. The patient in this case presented with intermittent visual symptoms 1 day after her procedure. Funduscopic examination demonstrated cotton wool spotting and then blanching consistent with retinal ischemia. The patient was placed on aspirin, and the symptoms resolved with no residual deficits.

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laser therapy. Unfortunately, she did not respond to treatment and thus was scheduled for intraophthalmic melphalan therapy. While she was under general anesthesia, a selective ophthalmic artery angiogram was obtained (Fig. 2). Chemotherapy (7.5 mg of melphalan) was then pulse-injected over 40 minutes directly into the ophthalmic artery under intermittent negative roadmap. Follow-up funduscopic examination while she was under anesthesia at 3 weeks after treatment demonstrated near-complete resolution of a large nasal retinoblastoma with clearing of all vitreous seeding.

**Discussion**

Left untreated, retinoblastoma progresses to metastatic disease in an average of 6 months; most metastases spread to the brain via the optic nerve. Primary enucleation remains the most common treatment worldwide, with 85%–95% of eyes treated in this manner. In recent years the emphasis has been on so-called globe preservation therapy, particularly for less advanced disease. Unfortunately, retinoblastoma, particularly unilateral retinoblastoma, is typically not detected until the eye is affected by advanced disease with vitreous seeding. Historically, these tumors have been the most difficult to control, as vitreous seeds have been shown by many authors to be both chemoresistant and unamenable to focal therapies. Even with aggressive multimodal therapy at highly experienced centers, enucleation rates are over 50% and rise to 100% once the patients fail to respond to this multimodal therapy.

In our cohort with advanced retinoblastoma refractory to multimodal therapy and awaiting enucleation, our treatment paradigm of melphalan infusion directly into the ophthalmic artery resulted in a dramatic decrease in the rate of enucleation to 23%. We have been unable to achieve such results even with aggressive combination therapy, and thus we now treat all refractory advanced retinoblastomas with intraophthalmic melphalan therapy.

Intraarterial infusion of chemotherapy for retinoblastoma was pioneered in Japan, where cultural attitudes preclude enucleation as a treatment option. Even in cases of advanced disease, families often prefer progression to brain metastases and even the death of the child over the removal of an eye. With this pressure for eye-preserving therapy, intraarterial infusions of chemotherapy were delivered into the supraorbital artery. A group from the National Cancer Center in Tokyo has reported on their extensive experience with nonselective intraarterial chemotherapy infusions into the carotid artery for retinoblastoma. Using a technique developed by Mohri, the Tokyo group inflated a balloon in the supraclinoid ICA, just distal to the take-off of the ophthalmic artery. They then infused melphalan from the cervical ICA with the

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**Fig. 1.** Funduscopic images obtained before treatment with intraophthalmic melphalan (upper) and 3 weeks after treatment (lower). Note the near-complete resolution of a large nasal retinoblastoma with clearing of all vitreous seeding.

**Fig. 2.** Selective ophthalmic artery angiogram showing filling of ophthalmic vessels without reflux of contrast into the ICA.
balloon inflated, diverting the drug into the ophthalmic artery. In their series of 176 patients, no bone marrow suppression or brain damage occurred; however, tumor control rates were not reported. In 2008 Abramson et al. described their experience in 9 patients treated with selective ophthalmic artery infusion of chemotherapy using doses ranging from 2 to 7 mg of melphalan. Grade III neutropenia developed in 1 patient, and conjunctival edema occurred in 3 patients, although it resolved without treatment in all 3. Seven (78%) of 9 patients avoided enucleation, and there were no cases of vitreous hemorrhage.

Treatment Protocol

We found a distinct difference in tumor control rates depending on whether the first infusion of melphalan was high dose (7.5 mg) or low dose (3 or 5 mg; Table 2). Enucleation rates varied according to the initial infusion dose, regardless of whether the tumor was retreated with high-dose melphalan. Overall enucleation rates were 36% in the tumors initially treated with low-dose melphalan, as compared with 0% in those initially treated with high-dose melphalan. It appears that a treatment protocol with an up-front lower dose in the hopes of possibly sparing a child a second procedure is not valid, as such a course has been associated with higher enucleation rates than those with a higher dose initially.

Furthermore, all serious ocular complications occurred in patients originally treated with the lower dose and then retreated with the higher dose of 7.5 mg. We had no cases of vitreous hemorrhage in patients treated with 7.5 mg up front, even if they were retreated with 7.5 mg.

Given our tumor control rates with this protocol, it seems reasonable to attempt to save a child from systemic chemotherapy and radiation by administering intraophthalmic melphalan as a first-line therapy for advanced retinoblastoma with vitreous seeding. In 1 patient in our series we offered up-front intraophthalmic melphalan before aggressive multimodal therapy. This patient responded to a single infusion of 7.5 mg of melphalan, and thus required no systemic chemotherapy, radiation, or local laser therapy. The tumor was stable at the 3-month follow-up. While not appropriate at this stage for less advanced disease, offering intraophthalmic melphalan as a first-line therapy may be reasonable considering the alternative of a prolonged course of multiple sessions of systemic therapy and focal laser treatments, particularly since a large proportion of patients do not respond to these treatments and thus end up being treated with intraophthalmic melphalan.

Delayed Vitreous Hemorrhage

Despite our overall excellent outcomes with regard to enucleation rates, intraophthalmic infusion of melphalan is not without morbidity. While the procedure itself in our hands is quite safe and the systemic toxicity is low, the delayed vitreous hemorrhages are more problematic because the hemorrhages block the focal consolidating laser. As described above, if the tumor demonstrates continued vascularity or abnormal margins, they are retreated with both intraophthalmic melphalan and repeat focal consolidating laser. If the eye has a vitreous hemorrhage at the 3-week follow-up examination, there are no more treatment options and the eye is enucleated. It is unclear exactly when these delayed hemorrhages occur since they are asymptomatic. We have begun to perform immediate posttreatment funduscopic examinations while the patient is still on the angiography table under general anesthesia, but we have not seen any evidence of acute hemorrhage thus far.

The mechanism behind these delayed vitreous hemorrhages is unknown. Melphalan may be toxic to the blood vessels of the tumor or the globe, predisposing the eye to hemorrhage. Moreover, in our series the 4 patients with delayed vitreous hemorrhage also showed persistent tumor activity, both at the time the hemorrhage was diagnosed funduscopically and on pathological analysis of the enucleated eye. This finding raises the possibility that the tumor itself has fragile neovascularization that is prone to bleeding. However, while vitreous hemorrhage in retinoblastoma has been reported, this complication is exceedingly rare. In fact, we have not seen a single case at our high-volume center. Thus, our 15% rate of delayed vitreous hemorrhage is substantially greater than that seen in patients not treated with intraophthalmic melphalan therapy.

It is important to note that even with the increased rate of vitreous hemorrhage, we are still substantially improving on the natural history of advanced retinoblastoma that is refractory to modern therapy. In fact, since the only practical consequence of delayed vitreous hemorrhage is that the eye is enucleated, it could be argued that there is no increased risk from the vitreous hemorrhages alone. Nonetheless, this complication has not been documented in previously published case reports of intraophthalmic melphalan therapy, despite the use of nearly identical treatment doses and protocols. It is thus important to counsel parents that although intraophthalmic melphalan therapy dramatically lowers enucleation rates, there remains a small group of tumors that will necessitate enucleation because of delayed vitreous hemorrhage.

Technical Nuances

A few specifics regarding our technique deserve mention. First, cannulation of the ophthalmic artery in a small child can be technically challenging. The artery is very small, and there is often a sharp turn right at the origin of the ophthalmic artery that must be negotiated (Fig. 2). We have found that positioning a straight microcatheter distal to the ophthalmic artery and then falling back into it is the most effective and safest way to cannulate the artery. The microcatheter is then advanced slightly to secure its position without being occlusive. As described above, we infuse from a position just inside the ostia of the ophthalmic artery rather than advancing the microcatheter down the length of the artery. It is not possible to inject contrast through the 4 Fr Terumo guide catheter once the microcatheter is inside; the roadmap must be obtained without the microcatheter. Despite these challenges, we were able to successfully cannulate the ophthalmic artery in all 26 of our treatment sessions.
Second, the infusion of the chemotherapy, like all intraarterial chemotherapy infusions, should be done in a pulsatile fashion to prevent streaming. Because of the laminar blood flow, slow, steady infusions will result in heterogeneous concentrations of drug in different parts of the cross-sectional area of the blood vessel, which then results in different concentrations in the branches downstream from the catheter tip, with some vessels receiving up to 5 times the expected dose. The technique of diastolic-phased pulsed infusion has been shown to reduce this phenomenon, resulting in a more uniformly distributed concentration of drug.

Conclusions

Direct intraophthalmic infusion of chemotherapy is an elegant solution to the difficult problem of advanced macular retinoblastoma with vitreous seeding. While the technical procedure is benign, the effect of direct intraophthalatic infusion of melphalan is not without risk as evidenced by our 15% rate of delayed vitreous hemorrhage. However, given the 100% enucleation rates in this cohort of retinoblastoma without intraophthalmic melphalan, this treatment modality represents a major advance in the treatment of these challenging cases and is at our center the treatment of choice for retinoblastoma with vitreous seeding that is refractory to treatment. Larger series are needed to determine the role of intraophthalmic melphalan therapy in retinoblastoma, particularly in patients with less advanced disease.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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References