Successful Treatment of Macular Retinoblastoma With Superselective Ophthalmic Artery Infusion of Melphalan

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ABSTRACT

Purpose: To report our experience with superselective ophthalmic artery infusion of melphalan (SOAIM) for macular retinoblastoma to obtain tumor control while preserving as much useful vision as possible.

Methods: Five patients with newly diagnosed unilateral retinoblastoma involving the macula were selected within a group of patients eligible for SOAIM as the primary treatment.

Results: The mean tumor basal dimension and thickness in this group of five patients with macular retinoblastoma were 11.6 and 12.3 mm, respectively. The stage at diagnosis ranged from II to VB (Reese-Ellsworth) or B to D (International Classification System). Tumor regression with SOAIM was achieved in all cases with regression patterns type I in four cases and III in one case.

Conclusions: SOAIM can be of value in the treatment of macular retinoblastoma. It may allow the salvage of the residual eyesight with a low rate of complications due to the local and systemic toxicity related to chemotherapy.

INTRODUCTION

Treatment options for retinoblastoma encompass: focal therapies (such as laser photocoagulation, thermotherapy, and cryotherapy), systemic (intravenous) chemotherapy, subconjunctival and intravitreal chemotherapy, intra-arterial superselective chemotherapy, brachytherapy with $^{125}$I or $^{106}$Ru plaques, external beam radiotherapy, and enucleation. Combining different treatments has resulted in significant improvement in survival rates, which have reached almost 99% in developed countries. However, the treatment of macular retinoblastoma still represents a challenge, particularly because of the trade-off between tumor-related and treatment-related visual loss. The central concern is the method of focal therapy, given the inherent risk of severe foveal damage and permanent visual loss.

Avoiding laser applications or any other type of focal treatment directly to the fovea has been advocated to decrease the risk of severe treatment-related central visual loss. For the same purpose, other authors have investigated the benefits and risks of
chemotherapy alone without focal consolidation, although it more often implies various serious toxic and side effects including, among others, myelosuppression, infections, and need for transfusion of blood products in up to 60% of cases. Friedman et al. published an extremely low rate of transfusions, but they reported a high rate (40%) of vincristine neurotoxicity and other systemic side effects.

Given the above, there is increasing interest in therapeutic approaches based on local administration of chemotherapeutic agents allowing the delivery of local high doses to the eye, thus avoiding systemic toxicity. Such approaches include subconjunctival injections of carboplatin, intravitreal injections of various chemotherapeutic drugs (including melphalan), and the more recent technique of superselective ophthalmic artery infusion of melphalan (SOAIM), possibly combined with topotecan and carboplatin, which usually requires a team of experts with highly specific skills to be performed. The purpose of this article is to report our experience with SOAIM for the treatment of unilateral sporadic retinoblastoma involving the macula.

**PATIENTS AND METHODS**

Five patients (Table 1) with newly diagnosed unilateral retinoblastoma involving the macula (the area localized within 3 mm from the foveola), who had...
been previously treated by SOAIM, were included in this study. The SOAIM eligibility criteria and protocol used in this study have been previously reported. In brief, standard therapy included a cycle of three infusions at an interval of 3 to 4 weeks each. Clinical and family history were recorded for each patient. For the clinical staging of each eye, both the International Classification (IC) and the Reese-Ellsworth classification (RE) were used. The size and location of each individual tumor focus at diagnosis were accurately recorded. The focus size was measured by one of the authors (TH) with reference to the largest basal diameter in millimeters under ophthalmoscopic examination. Ophthalmic examination was performed.

**Figure 1.** Patient 1. Ophthalmoscopic appearance of the fundus oculi (A) at diagnosis and (B) after 29 months of follow-up.

**Figure 2.** Patient 2. Ophthalmoscopic appearance of the fundus oculi (A) at diagnosis and (B) after 11 months of follow-up.

**Figure 3.** Patient 3. Ophthalmoscopic appearance of the fundus oculi (A) at diagnosis and (B) after 10 months of follow-up.
1 to 7 days before each intra-arterial treatment and included external evaluation, visual acuity testing if possible (according to patients’ age and cooperation), and anterior segment and complete fundus examination under anesthesia, including Retcam digital photography (Massie Industries, Dublin, CA) (Figures 1-5), and B-scan ultrasound at 12 mHz (B Scan Plus; Accutome Inc., Malverne, PA). Systemic evaluation included an interval history, weight and height measurements, and complete blood counts performed between visits and repeated if necessary. Follow-up with head and orbit gadolinium-enhanced magnetic resonance imaging was performed when clinically indicated. The follow-up starting from the date of the first SOAIM ranged from a minimum of 10 months to a maximum of 34 months (mean: 19 months, median: 11 months).

**RESULTS**

All patients received an entire SOAIM (ie, a cycle of three intra-arterial injections).

Patient 1 presented with exotropia and leukokoria in the right eye and was classified as Group II (RE) or B (IC). The tumor seemed to result from malignant transformation of a retinoma involving the posterior pole (Figure 1A). After the first intra-arterial infusion (melphalan 5 mg), a reduction of approximately 80% of the initial size of the tumor and an increased calcific component were noted. Transient adverse ocular events were mild periorbital skin hyperemia and edema. Twenty-nine months later (Figure 1B), ophthalmoscopy of the tumor mass of the posterior pole showed a type I complete remission with a large surrounding halo of chorioretinal atrophy.

Patient 2 presented with exotropia in the right eye and was classified as Group III (RE) or D (IC). The tumor mass at the posterior pole with a diameter of $10 \times 12$ mm was adjacent to the optic nerve, which showed free edges. There were two small hemorrhages at the tumor apex. Noticeably, the dilation of the superonasal branch of the oph-
thalamic artery disappeared temporally in the mass (Figure 2A). An impressive regression of the tumor mass was evident after the first intra-arterial infusion. The patient did not develop any adverse ocular event. Eleven months later (Figure 2B), a type I regression was evident on ophthalmoscopy.

Patient 3 presented with exotropia in the right eye and was classified as Group II (RE) or D (IC). At presentation (Figure 3A), a tumor mass with a diameter of approximately 10 × 10 mm involved the posterior pole: it was dome-shaped and finely vascularized on the surface with a large feeder vessel that disappeared into the mass. The macula was involved from the bottom edge of the mass. Tumor reduction occurred after the first intra-arterial infusion (melphalan 4 mg), including a coarctation that drew away by at least 3 mm from the foveolar area. Mild hemorrhages on the papillomacular bundle were also evident. Ten months later (Figure 3B), the tumor mass was further reduced in size, showing a type I regression.

Patient 4 showed a weak red reflex in the left eye at presentation and was classified as Group II (RE), with focal subretinal dissemination, or D (IC). Ophthalmoscopic examination (Figure 4A) showed a large mass of 12 × 10.5 mm at the posterior pole with a large superotemporal feeder vessel, a yellowish pigmentation on the papillary side of the mass, and pigment migration around the lower area. Subretinal dissemination was also evident from hours 4 to 5, and was treated by cryotherapy. After only one SOAI of melphalan (4 mg), there was a marked coarctation of the large mass, which shrank to 6.7 × 8.2 mm. The feeder vessel and the subretinal dissemination also showed a reduction, and the tumor mass underwent a type III regression. Transient adverse ocular events included mild periorbital skin hyperemia and edema, ptosis, and eyelid rash. Eleven months later (Figure 4B), the regression pattern previously achieved was still preserved but a marked chorioretinal atrophy had developed.

Patient 5 presented with leukocoria in the right eye and was classified as Group VB (RE) or D (IC). Retinoblastoma. At presentation, the patient showed a dome-shaped tumor of approximately 15 × 18 mm in the papillomacular area. Along the bottom edge, three fine elements of epitumoral seeding with a “grass in the broth-like” appearance were also evident. With the first intra-arterial infusion, a marked reduction of the mass to 9 × 10.5 mm was obtained. A transient eyelid rash was also observed as an adverse ocular event. Three months after the end of a complete cycle of intra-arterial treatment (Figure 5A), a type I complete remission (including a “calcified cauliflower appearance” and marked pigment migration) was achieved. Thirty-four months later (Figure 5B), a marked chorioretinal atrophy and retinal pigmented epithelium alterations were present.

Globally, SOAIM was well tolerated, without major side effects (eg, death, stroke, and seizures). There were no dissections, occlusions, or hematoma in both the carotid and femoral arteries, and no occlusion of the central retinal arteries and/or abnormalities in cornea, anterior chamber, or lens.

All local adverse events were transient: two cases (40%) of mild periorbital skin hyperemia and edema, two cases (40%) of eyelid rash, one case (20%) of papillomacular bundle mild hemorrhage, and one case (20%) of ptosis. Two patients (40%) had delayed choroidal ischemia and developed choriotinal atrophy (one of these also developed alterations of the pigmented epithelium).

All eyes were also treated with transpupillary thermotherapy during or after the intra-arterial treatment cycle. One eye (patient 4) also received cryotherapy for a slight exudation in the inferior retinal periphery and another (patient 5) was also treated with argon laser to consolidate the regression in the peripheral edge of the tumor. Types I and III of regression of the tumor foci were obtained. All patients are alive and free of metastatic disease. None of the eyes has been enucleated.

DISCUSSION

Conservative retinoblastoma management is a complex task that depends on many variables, including tumor laterality and size, macular involvement, vitreous or subretinal seeding, general patient age and health, genetic make-up, and the needs and expectations of parents and relatives.25,26

Several treatment options can be offered to children with unilateral sporadic retinoblastoma, including focal therapies, chemoreduction (with intra-arterial chemotherapy, among others), subconjunctival and intravitreal chemotherapy, brachytherapy with 125I or 106Ru plaques, external beam radiation, and enucleation. More controversial is the optimal treatment of tumors located in the posterior pole. Despite the widespread agreement on treating large macular retinoblastoma with enucleation,
particularly when associated with extensive subretinal fluid or vitreous seeding, Abramson et al.27 concluded that, unlike radiation or systemic chemotherapy, intra-arterial chemotherapy can usually prevent the need for enucleation in naive eyes with advanced intraocular retinoblastoma with seeding, especially if the seeding is in the subretinal region. This approach seems to be less effective in previously treated eyes when subretinal seeding is present (50% at 2 years), but may be more effective in eyes that failed to respond to previous systemic chemotherapy and only show vitreous seeding. In the current investigation, we used intra-arterial chemotherapy in a case (patient 5) with advanced macular retinoblastoma (RE Group VB) with epitumoral seeding, and this resulted in a type I complete remission of the tumor mass.

Less advanced tumors are currently treated with non-enucleation procedures, including chemoreduction associated with foveal-sparing thermotherapy,28 which allows better tumor control than chemotherapy alone. However, the risk/benefit ratio of these strategies should be carefully considered for all children with macular retinoblastoma.

Interestingly, the current investigation shows that even patients with less advanced disease, such as our group II (RE) retinoblastoma, may be usefully treated with SOAIM and this confirms the results obtained in the same cases by other authors.25,26 The risk of vasculopathy of the ophthalmic, retinal, and choroidal vessels following intra-arterial chemotherapy has been described in the literature. Gobin et al.29 reported 4 cases of avascular retinopathy with total visual loss in their series of 78 patients (95 eyes).

In their series of 16 patients successfully cannulated, Shields et al.30 reported occlusive vasculopathy in the ophthalmic artery in 4 cases (permanent in 3 cases, temporary in 1 case), diagnosed by funduscopy (confirmed on fluoroscopy) in 3 of those cases. Moreover, they noted subtle retinal pigment epithelial mottling in 9 cases that slowly evolved to later-onset underlying choroidal atrophy in 5 cases. Using high-resolution fluorescein angiography in another report,31 the same group found that 46% of eyes had some degree of intraocular vascular alteration that was subclinical in most cases. They recommended using fluorescein angiography in all cases to detect vascular flow alterations after intra-arterial chemotherapy.

Vajzovic et al.32 treated 12 eyes of 10 children with advanced retinoblastoma (stage VB of RE, D of IC); 11 eyes (of 9 patients) had previously failed traditional management and underwent intra-ophthalmic artery infusion of melphalan as an alternative of enucleation. They reported striking regression of tumor and subretinal and vitreous seeds early in each case; however, 3 of the 12 eyes (25%) were enucleated for suspected tumor recurrence (confirmed on histopathologic examination). They described the following local toxicities: microemboli to the retina and choroid (8%), vitreous hemorrhage (25%), and myositis (8%).

The specific pathogenesis of the vascular insult remains unknown, but it could be due to catheter-related insult to the endothelium, chemotherapy toxic effects on the vessel or specifically the endothelium, or embolization from foreign body contamination or chemotherapy precipitation. In our series, no clinically visible emboli were documented and fluoroscopy before and after intra-arterial chemotherapy has confirmed the lack of catheter-related dissection or macroscopic trauma. The chorioretinal atrophy developed after the second infusion of melphalan in both cases of our series.

The treatment of macular retinoblastoma is particularly challenging because of the trade-off between tumor control and the potential for tumor-related and treatment-related visual loss. To our knowledge, this is the first clinical study to determine whether and how SOAIM allows tumor control in macular retinoblastomas. Based on our experience, we conclude that SOAIM is effective in the treatment of macular retinoblastoma, although more data are needed to reach statistical significance. Melphalan superselectively delivered to the ophthalmic artery may allow the salvage of eye globes that would otherwise be enucleated, with a low rate of complications due to local and systemic toxicity. Although more data are necessary, particularly regarding the need of supplementary chemotherapy in selected cases, according to the staging, longer follow-up investigations, potential extensions of the indications for SOAIM, accurate monitoring and evaluation of side or undesired effects, and standardization of the therapeutic protocol, we suggest that SOAIM may represent a potentially useful approach to the treatment of retinoblastoma, with no apparent limitations due to the extension of the disease at diagnosis.

REFERENCES