



Intracameral Chemotherapy for Globe Salvage in Retinoblastoma with Secondary Anterior Chamber Invasion



The presence of anterior chamber seeding (ACS), whether primary (1%) or secondary, is commonly treated by enucleation. Considering the new frontiers of conservative management of very advanced retinoblastoma, the reported incidence of secondary ACS leading to conservative failure has progressed from 6% after chemoreduction to 67% after intra-arterial chemotherapy (IAC).¹

Anterior chamber seeding is considered an intractable form of retinoblastoma regardless of the treatment used because of the hypoxic radio-resistant nature of the seeds and inability to reach tumoricidal concentrations in the aqueous using known routes of chemotherapy administration. Successful attempts to treat ACS were reported only recently and concerned patients with primary ACS in diffuse anterior retinoblastoma of retinal origin by intracameral chemotherapy (ICC)² and of extra-retinal origin by brachytherapy.³

In this retrospective review approved by the ethical committee of Vaud, Switzerland (authorization no. 2016-00149), 12 consecutive patients with ACS treated with ICC were identified between November 2011 and October 2016. One case was excluded with primary ACS class III (pseudo-hypopion) resulting from anterior diffuse retinoblastoma published previously² with an event-free follow-up of 5.5 years. The study population consisted of 11 eyes with secondary ACS from 11 heavily pretreated patients for whom advised enucleation was refused by the parents, including 10 patients with relapse referred from other centers. There were 4 eyes with unilateral and 7 eyes with bilateral retinoblastoma, of which 4 were remaining eyes after previous enucleation of the fellow eyes. The demographic characteristics and the treatment received before ICC, as well as ACS classification, relapses, and concomitant ultrasound biomicroscopy features, are shown in [Table S1](#) (available at www.aaojournal.org).

Anterior chamber seeding was classified as class I in 5 eyes, class II in 5 eyes, and class III in 1 eye ([Fig 1A–F](#)). According to the integrity of anterior hyaloid, 2 distinct mechanisms of tumor progression into the anterior segment could be distinguished: (1) transhyaloid infiltration into the posterior chamber secondary to vitreous seeds attached to the anterior hyaloid in 3 eyes (no peripheral primary or secondary retinal tumors) or to the anterior progression of a peripheral parietal tumor overlying the pars plana in 4 eyes ([Fig 1G, I](#)); and (2) invasion via a disrupted anterior hyaloid of iatrogenic origin, that is, pars plana vitrectomy ([Fig 1K, L](#)), and clear corneal intracapsular lensectomy in 2 eyes each. Anterior chamber seeding was isolated (9 eyes) or associated with an anterior uveal infiltration (2 eyes) as assessed by ultrasound biomicroscopy.

Intracameral chemotherapy with melphalan was administered (concentration of 15 or 20 µg/ml, the lower concentration used

initially and the higher concentration used in case of ACS relapse/persistence) as previously described.² All but 3 eyes (vitrectomized with silicone oil or postintraocular lensectomy, see [Table S1](#), available at www.aaojournal.org) received concomitant intravitreal chemotherapy at least once via the pars plana with 20 to 30 µg of melphalan at a concentration of 200 µg/ml to treat the underlying vitreous disease or, if absent, to prevent cross-contamination between the aqueous and the vitreous. Tumor control was monitored clinically by slit-lamp examination as well as in the iterative aqueous taps by cytopathology and by cell culture when available.² Intracameral chemotherapy was continued as long as the cytopathology or cell culture remained positive and at least 1 additional injection was given after a negative result.

Complete aqueous seeding regression was initially obtained in all eyes after a mean of 0.7 months (range, 0.2–1.3) as assessed clinically and by negative cytopathology and cell culture, after a mean number of 4.3 injections (range, 2–7) with a mean dose of 6.3 µg (range, 2.9–15) per injection. Higher doses corresponded to a greater quantity of aqueous humor withdrawn in cases with disrupted hyaloid (mean 0.46 ml compared with 0.24 ml with the hyaloid intact), indirectly confirming disruption of the hyaloid. Anterior chamber seeding class I required notably less mean 3.2 injections compared with 5.2 injections in classes II and III. Treatment during or after ICC, ICC-related complications, globe preservation, functional results, and histopathology of the enucleated eyes are summarized in [Table S2](#) (available at www.aaojournal.org).

Eye preservation was achieved in only 25% (1/4) of cases with disrupted anterior hyaloid versus 71% (5/7) with intact anterior hyaloid, including all 4 remaining eyes after previous enucleation of the fellow eyes. The absence of anterior hyaloid in the former group of 4 eyes could have influenced negatively the outcome by 2 mechanisms: (1) by preventing the achievement of a tumoricidal concentration in the anterior segment through dilution of the ICC in the posterior segment or (2) by favoring or maintaining cross-contamination between the posterior and anterior segment. In the latter group of 7 eyes with apparently intact anterior hyaloid, 2 eyes (cases 5 and 10) underwent enucleation for progressive disease after a retention time of 2.8 and 1.0 months, respectively, after the first ICC. Failure in case 5 was likely related to the extreme aggressiveness of the N-myc amplification genotype, whereas in case 10, secondary enucleation was decided on the basis of disease progression in an eye devoid of visual potential and with an obscured optic disk. In total, enucleation was performed in 5 cases after a mean retention time of 8.8 months (range, 1.0–20.7). In 1 eye (case 5), histopathology revealed higher risk factors, supporting the indication for systemic adjuvant chemotherapy ([Table S2](#), available at www.aaojournal.org) and remained event-free over a follow-up of 24 months. Patient number 1 received 2 courses of carboplatin-etoposide intravenous chemotherapy, considering that transconjunctival pars plana vitrectomy had been performed in the context of unsuspected diffuse infiltrating retinoblastoma before his referral. Conservative treatment

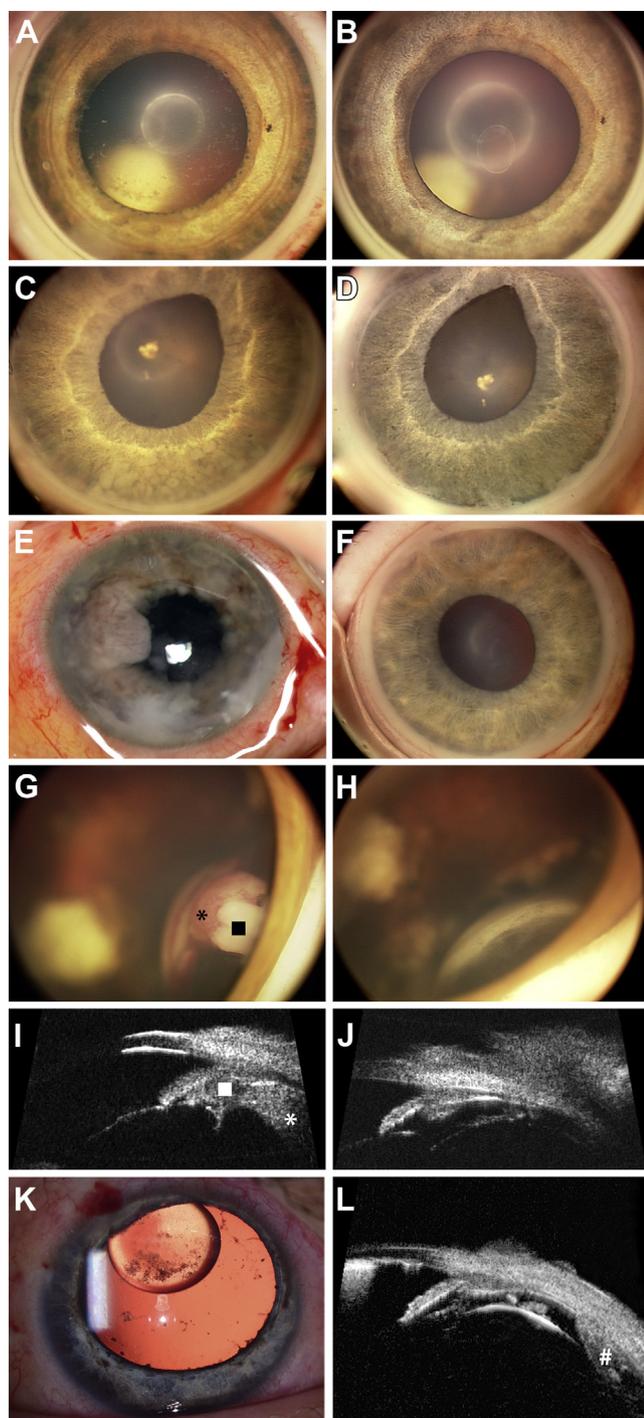


Figure 1. Anterior chamber photography with aqueous seeding class I (first row: case 2), class II (second row: case 3), and class III (third row: case 11) before (A, C, E) and after (B, D, F) ICC. Note the diffuse iris hypochromic heterochromia after ICC (B, D). The pupillary deformation (C, D) is iatrogenic after intracapsular extraction of the lens. G–L, RetCam images and ultrasound biomicroscopy longitudinal sections featuring intact (G–J) or disrupted (K, L) anterior hyaloid in 2 phakic eyes from cases 2 and 1, respectively (Tables S1 and S2, available at www.aaojournal.org). G, I, Case 2 before treatment: retinal tumor recurrence across the ora serrata (black and white asterisks) over the pars plana with presumed transhyaloidal invasion of the posterior chamber (black and white squares) via Petit's canal. H, J, Case 2 after treatment (ICC and brachytherapy) showing complete response (H):

was attempted given that visual function was preserved (20/30) with fovea and optic nerve intact. No adjuvant systemic chemotherapy was given to any of the other patients, considering that the prognostic value of aqueous seeding or anterior uveal invasion such as iris or corpus ciliaris involvement is no longer considered a high risk for metastasis.^{4,5} Salvaged eyes have a mean event-free follow-up of 17 months (range, 4–36). All patients are alive without metastasis at a mean follow-up of 24 months (range, 12–54).

In conclusion, ICC concomitant with other treatments, offers an alternative to enucleation in selected cases of retinoblastoma with secondary ACS. Although these are encouraging results, further studies with longer follow-up are necessary to assess the safety and long-term efficacy of this new targeted modality.

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regression of retinal tumor with posterior chamber tumor-free and no apparent interruption of the anterior hyaloid (J). K, L, Anterior segment RetCam image of case 1 showing the presence of silicone oil and dust (K). Silicone oil in the anterior and posterior chambers is shown on longitudinal ultrasound biomicroscopy section (L). Note 2 visible spheres in the posterior chamber at the surface of the highly echogenic silicone bubble. Hashtag (#) indicates the thickened retina up to the ora serrata, corresponding to anterior extension of the diffuse infiltrating retinoblastoma.

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Topical Cidofovir for Treatment-Refractory Ocular Surface Squamous Neoplasia



Ocular surface squamous neoplasia (OSSN) is defined as a group of dysplastic, preinvasive, and malignant squamous lesions involving the cornea and conjunctiva. Management of OSSN varies, and typically is governed by lesion size, distribution, and pathologic severity. Treatment incorporates surgical excision with adjuvant cryotherapy to margins, topical chemotherapy, or both, the latter commonly with mitomycin C and 5-fluorouracil.¹ More recently, the application of topical interferon alfa-2b has been used successfully for treating OSSN. Yet despite the prevailing contemporary standard of care, recurrence remains high at up to 53% of cases.¹

Human papilloma virus (HPV) has been implicated as an etiologic agent in the pathogenesis of OSSN. We demonstrated that approximately 6.5% of OSSN specimens showed positive results for a high-risk HPV serotype (HPV-16), detection of which corresponded with more severe pathologic OSSN types, namely squamous cell carcinoma.² Cidofovir is an antiviral with activity against different double-stranded DNA viruses, including HPV, and has been used previously to treat HPV-associated lesions.³

This single-center, retrospective, interventional case series recruited 6 patients with treatment-refractory OSSN. Patients satisfied inclusion criteria if they possessed biopsy-proven diagnoses of OSSN before cidofovir administration and were treatment refractory to surgery, adjuvant cryotherapy, and an additional topical agent. Patients were excluded if additional or alternate diagnoses on biopsy were identified. Formalin-fixed paraffin-embedded tissues and ThinPrep (Cytoc Corp; Marlborough, MA) specimens were analyzed for HPV presence using a hybrid-capture assay.² Details of our HPV detection methodology can be found in [Appendix 1](#) (available at www.aaojournal.org).

A chart review of all patients treated with topical cidofovir (2.5 mg/ml thrice daily) between 2014 and 2016 was conducted. Topical cidofovir vials were compounded at an external pharmacy, and patients were treated for at least 4 weeks. Tumor regression was diagnosed with slit-lamp biomicroscopy and photography and, if required, repeat histopathologic analysis. Recurrence was monitored after first documented instance of tumor resolution. Institutional ethics review board approval was obtained for this

study. This study was approved by the South-Eastern Sydney Area Health Service Human Research Ethics Committee (Eastern Section) 15/200 and was performed in accordance with the tenets of the Declaration of Helsinki.

Five men and 1 woman (mean age, approximately 82.1 years) with treatment-refractory OSSN were treated with 2.5 mg/ml topical cidofovir (1 drop thrice daily) for 4 to 9 weeks ([Table 1](#); [Fig S1](#), available at www.aaojournal.org). Patients responded to topical cidofovir at varying times, with first observation for tumor clearance ranging between 24 and 60 days. Patients thus continued topical cidofovir until the end of the week after tumor clearance was first observed. Our patients had been previously managed for 1337 days (mean) of excisional biopsy, adjuvant cryotherapy, topical interferon alfa-2b and retinoic acid, intraleSIONal interferon, oral cimetidine, topical mitomycin C cycles, or a combination thereof before commencing topical cidofovir. A mean tumor-free follow-up of approximately 454 days (range, 222–876 days) was achieved from our case series of 6 patients, with tumor clearance identified in 5 of 6 eyes affected and no observable recurrence even at present. One eye demonstrated conjunctivitis and punctal stenosis during treatment with cidofovir that settled on treatment cessation. Two lacrimal punctum plugs were placed as prophylaxis (patient 4). All 5 treatment specimens obtained before cidofovir administration were analyzed for high-risk HPV presence, and HPV-16 was identified in 1 patient (patient 4) only. No HPV detection after treatment was performed.

Conundrums that prevent optimal OSSN control include invisible disease with lacrimal system metastases and multifocal limbal disease. Topical therapy represents a solution for mitigating these, being able to treat the entirety of the ocular surface and inconspicuous spread within the lacrimal drainage system. Unfortunately, contemporary topical chemotherapeutic agent application (mitomycin C or 5-fluorouracil drops) is associated with transient ocular adverse effects, and occasionally destructive sight-limiting complications.¹ Topical interferon alfa-2b monotherapy represents an alternative with a decreased side-effect profile and improved tumor-free follow-up.¹ We previously demonstrated in an 89-patient study excellent tumor clearance of approximately 97.8% and tumor-free follow-up of approximately 51.5 months when using topical interferon alfa-2b and all-trans retinoic acid combination therapy.⁴ Despite the excellent results, approximately 2% of patients demonstrated recurrent disease, and we hypothesized that a viral coinfection with HPV may be contributing toward therapy-resistant diseases.

We observed only 1 case each of transient conjunctivitis and punctal stenosis, both of which resolved after treatment cessation and lacrimal punctum plugging. Because of the known toxicity of cidofovir, other antiviral agents may be warranted that have less impact on the lacrimal drainage apparatus, or lacrimal plugs may be used as an adjunct. We observed that most of our patients (n = 5) showed complete resolution after topical cidofovir application with an average tumor-free follow-up of approximately 454 days. More severe grades of OSSN (corneal–conjunctival intraepithelial neoplasia II/III; patients 2–5) were more likely to respond to topical cidofovir compared with lower-grade tumors (corneal–conjunctival intraepithelial neoplasia I; patient 1), which may be the result of a correlation between more severe tumor types and viral coinfection.² However, 1 patient (patient 6) demonstrated observable tumor clearance despite histopathologic identification as a benign papilloma.

Only 1 specimen obtained before cidofovir treatment showed positive results for HPV-16, although there exist factors that may have