Original Article

Periocular topotecan for vitreous seeds in retinoblastoma

Purnima R Sthapit, Raksha Rao, Santosh G Honavar

Purpose: Refractory or recurrent vitreous seeds account for a large proportion of failure of eye salvage in retinoblastoma. The purpose of this study is to evaluate the efficacy of periocular topotecan (POT) in the management of vitreous seeds in retinoblastoma. **Methods:** Retrospective, interventional study of patients with retinoblastoma with vitreous seeds who received POT concurrent with intravenous chemotherapy (IVC). **Results:** Thirty-eight eyes of 35 patients received POT. Five eyes (13%) belonged to International Classification of Retinoblastoma group C, 23 eyes (61%) belonged to group D, and 10 eyes (26%) belonged to group E. Primary treatment included IVC with a combination of carboplatin, etoposide, and vincristine for a mean of 6 cycles (median 6; range 6–9). Concurrent to IVC from the fourth cycle onward, all patients received POT. Focal vitreous seeds were present in 20 eyes (53%) which received a mean of 3 injections (median 3; range 1–7). Diffuse vitreous seeds were present in 18 eyes (47%) which received a mean of 4 injections (median 5; range 1–7). At a mean follow-up of 8.5 months (median 5 months; range 1–15 months), regression of focal and diffuse vitreous seeds was achieved in 16 eyes (80%) and 8 eyes (44%), respectively. In all, 24 eyes (63%) had complete remission of vitreous seeds with POT given concurrently with IVC. Eye salvage was possible in 19 eyes (95%) with focal vitreous seeds and 12 eyes (68%) with diffuse VS. Enucleation was necessary for persistent vitreous seeds and viable tumor in five eyes (13%), viable tumor alone in one eye (0.02%), and recurrent vitreous seeds in one eye (0.02%). None of the patients developed systemic metastasis. **Conclusion:** POT administered concurrent with IVC is safe and effective in the initial management of vitreous seeds.

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Vitreous seeds continue to pose a challenge in the eye salvage therapy of retinoblastoma.[1,2] In a study by Shields *et al*., the authors observed that eye salvage in International Classification of Retinoblastoma (ICRB) groups A, B, and C using intravenous chemotherapy (IVC) alone was 100%, 93%, and 90%, respectively.[3] In eyes with diffuse vitreous seeds, the eye salvage rate with IVC was a mere 30%.[3] The avascularity of the vitreous precludes the penetration of intravenously administered chemotherapy which leads to persistent seeds despite the regression of the main tumor, thus contributing to failure of IVC in advanced cases.[4] For this reason, intravitreal chemotherapy has gained popularity in the management of eyes with refractory and persistent vitreous seeds.[5-7] Safety-enhanced intravitreal injection involves triple freeze–thaw cryotherapy of the carefully chosen injection site.[4,8] In general, intravitreal injections are given after achieving a significant reduction in tumor volume by systemic or intra-arterial chemotherapy to minimize the risk of extraocular extension of any viable tumor through the needle tract.[8] Hence, for vitreous seed control in the active phase of the disease, periocular chemotherapy offers a better alternative.

The use of periocular carboplatin has been reported in the literature, and it has been observed that a high intraocular concentration of carboplatin is attained with minimal systemic side effects.[9-12] Chemotherapy by the trans-scleral route is known to achieve a drug concentration of about 6–10 times higher than that achieved by the intravenous route within 30 min of injection.[13] However, reports on the use of periocular carboplatin suggest serious local adverse effects including orbital fibrosis and optic nerve atrophy.[10-12] In contrast, a dose of 2 mg of periocular topotecan (POT) has been reported to be effective and safe.[14] Several studies in the past have reported the effect of POT on retinoblastoma regression, but to the best of our knowledge, this is the first study specifically aimed at its effect on vitreous seeds.[14-17] Herein, we report the efficacy of topotecan injection by periocular route with concurrent systemic chemotherapy in the management of focal and diffuse vitreous seeds.

Methods

This is a retrospective, noncomparative, interventional study conducted from July 2013 to February 2017. Our objective was to study vitreous seed regression and eye salvage. The study

National Retinoblastoma Foundation, Department of Ophthalmic and Facial Plastic Surgery and Ocular Oncology, Centre for Sight Superspeciality Eye Hospital, Hyderabad, Telangana, India

Correspondence to: Dr. Santosh Honavar, Centre for Sight Superspeciality Eye Hospital, Road No. 2, Banjara Hills, Hyderabad - 500 034, Telangana, India. E-mail: santosh.honavar@gmail.com

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setting was an integrated retinoblastoma referral center at a tertiary care eye hospital. Institutional review board approval was obtained.

The data were collected from our comprehensive medical record files and serial fundus images of the patients were taken during the course of treatment. Demographic data recorded from the first visit to the hospital included age at diagnosis, gender, race, laterality, and the eye involved. All patients were grouped under ICRB classification after detailed examination under anesthesia. The number of tumors per eye, the basal diameter, and height of each tumor were recorded. The presence and extent of subretinal seeds and vitreous seeds were assessed and classified as focal if located 3 mm or less from the main tumor and diffuse if located more than 3 mm away. Vitreous seeds were further classified into primary (present at the time of diagnosis), secondary (developed later during the course of treatment), persistent (residual even after completion of systemic chemotherapy for main tumor), and recurrent (reappearing after a disease-free interval). The morphology of the vitreous seeds was also noted (dusts, spheres, or clouds). The location of vitreous seeds was recorded as being free floating in vitreous cavity, deposits on ciliary body, or resting on prehyaloid or retrohyaloid space.

All the patients in the study received IVC with a combination of standard dose vincristine, carboplatin, and etoposide for a minimum of six cycles. Chemotherapy was extended if there were residual or recurrent retinal tumors beyond six cycles in patients with potential eye and vision salvage. Focal treatment with transpupillary thermotherapy and cryotherapy was used for the main tumor and recurrent subretinal seeds. Those with focal and diffuse vitreous seeds, which were persistent or appeared after the third cycle of IVC, received a variable number of POT injections. The procedure involved identification and marking of the eye to be injected, followed by sterilization of the periocular area with 5% povidone iodine solution. Wire speculum was placed and eyeball rotated and fixed at temporal gaze with a tooth forceps. Under direct visualization of microscope, 2 mg (2 mL) of topotecan was injected at the inferonasal quadrant in the posterior subtenon's space using a 27-guage needle. After withdrawing the needle, compression was applied to the injection site with a cotton-tipped applicator for a minute and the eye was padded with an antibiotic ointment for 24 h. A tapering dose of steroid eye drops, cyclopentolate 1% eye drop, and ibuprofen syrup were prescribed.

All patients were examined every 4 weeks under anesthesia, and POT was continued concurrent with IVC. Intravitreal topotecan was used in those whom vitreous seeds persisted or recurred after the completion of IVC. The outcome in every case and decision in the management was done by an experienced ocular oncologist. The clinical data were analyzed with regard to the outcome measures – vitreous seeds' regression pattern in focal and diffuse types, number of periocular and additional intravitreal injections required in each group, and the percentage of eyes salvaged.

Results

There were a total of 38 eyes of 35 patients who received POT for focal or diffuse vitreous seeds. The mean patient age at the time of diagnosis of retinoblastoma was 24 months (median 22 months; range 3–77 months). Of the 35 patients, 19 (54%) had bilateral disease [Table 1]. They were classified according to ICRB grouping as shown in Table 2. Four patients in group E also had clinical high-risk factors including anterior chamber seeds in one eye (3%), neovascularisation of iris in two eyes (6%), and NVG in one eye (3%). Of the 38 eyes, endophytic tumor and mixed endo-exophytic tumor were seen in 17 eyes each (45%), exophytic tumor in 2 eyes (6%), and diffuse infiltrative retinoblastoma in 2 eyes (6%). There was more than one tumor in 12 eyes (32%).

The mean maximum basal diameter of the largest tumor was 14.3 mm (median 14 mm; range 7–20 mm) and the mean tumor thickness was 10.7 mm (median 11 mm; range 3–18 mm). Seven eyes (18%) had a single large tumor filling most of the vitreous cavity. Vitreous seeds were focal in 20 eyes (53%) and diffuse in 18 eyes (47%) which were present at different times during the course of the disease. Vitreous seeds were located in the prehyaloid area in six eyes (16%), retrohyaloid area in one eye (3%), whereas the rest of the 31 eyes (81%) had free floating seeds. Ciliary body seeds along with vitreous seeds were noted in four eyes (11%). Seven eyes (18%) had focal and 11 eyes (29%) had diffuse concurrent subretinal seeds, believed to be a source of new tumor formation and recurrent vitreous seeds.[8,18]

In all, a total of 150 POT injections were given to the 38 eyes in the study duration. Eyes with focal vitreous seeds required a mean of 3 injections (median 2; range 1–7), whereas those with diffuse vitreous seeds required a mean of 4 injections (median 5; range 1–7), with complete regression attained in 16 eyes (80%) and 8 eyes (44%) [Figs. 1-3], respectively. The results are compared and summarized in Table 3. In all, 24 eyes (63%) had complete remission of vitreous seeds with POT. Barring conjunctival chemosis in two eyes (5%) and eyelid edema in five eyes (13%), no other complications were noted after POT injections.

For persistent vitreous seeds, eight eyes (21%) required an additional treatment with intravitreal topotecan injection to

Table 1: Periocular topotecan for focal and diffuse vitreous seeds in retinoblastoma: patient demographics

Demographics	Patients, *n*=35 (%)
Age, months	
Mean (median, range)	24 (22, 3-77)
Race	
Asian Indians	35 (100)
Sex	
Male	22 (63)
Female	13 (37)
Heredity	
Nonfamilial	33 (94)
Familial	2 (6)
Laterality of retinoblastoma	
Unilateral	16 (46)
Bilateral	19 (54)
Eye in which the injection was administered, *n*=38 eyes	
Right eye	14 (37)
Left eye	24 (63)

Table 2: Periocular topotecan for focal and diffuse vitreous seeds in retinoblastoma: clinical features

Clinical characteristics	Eyes, *n*=38 (%)
International Classification of Retinoblastoma group at the time of the diagnosis of retinoblastoma	
Group C	5 (13)
Group D	23 (61)
Group E	10 (26)
Type of retinoblastoma	
Exopthytic	2 (6)
Endophytic	17 (45)
Mixed	17 (45)
Diffuse infiltrative	2 (6)
Basal diameter of the largest tumor, mm	
Mean (median, range)	14.3 (14, 7-20)
Tumor thickness, mm	
Mean (median, range)	10.7 (11, 3-18)
Chemotherapy cycles	
Mean (median, range)	6 (9, 6-9)
Extent of vitreous seeds	
Focal	20 (53)
Diffuse	18 (47)
Morphology of vitreous seeds^	
Dusts	5 (13)
Spheres	19 (50)
Clouds	15 (39)
Location of vitreous seeds*	
Prehyaloid	6 (16)
Retrohyaloid	1 (3)
Free floating in vitreous	31 (81)
Ciliary body	4 (11)
Periocular topotecan injections for focal seeds	
Mean (median, range)	3 (2, 1-7)
Periocular topotecan injections for diffuse seeds	
Mean (median, range)	4 (5, 1-7)
Concurrent laser transpupillary thermotherapy or cryotherapy for the control of minimal residual retinal tumor or subretinal seeds	
Yes	38 (100)
No	0 (0)

^One eye had more than one type of seeds. *Four eyes had tumor seeds along the ciliary body in addition to the vitreous seeds

Table 3: Periocular topotecan for focal and diffuse vitreous seeds in retinoblastoma: outcomes

Outcomes	Eyes, *n*=38 (%)
Duration of follow-up since last injection, months	
Mean (median, range)	8.5 (7, 1-15)
Initial response of vitreous seeds	
Regression	24 (63)
Persistence	14 (37)
Management of persistent vitreous seeds, *n*=14 eyes	
Intravitreal topotecan	8 (21)
External beam radiotherapy	1 (2)
Enucleation	5 (13)
Management of recurrent vitreous seeds, *n*=18 eyes	
POT	5 (28)
IVC + POT	4 (22)
Intravitreal topotecan	8 (44)
Enucleation	1 (5)
Vitreous seed regression in total	24 (63)
Eyes with focal vitreous seeds	16 (80)
Eyes with diffuse vitreous seeds	8 (44)
Eye salvage in total#	31 (82)
Eyes with focal vitreous seeds	19 (95)
Eyes with diffuse vitreous seeds	12 (68)
Life salvage	35 (100)
Complications	
Ocular	7 (18)
Eyelid edema	2 (5)
Conjunctival chemosis	5 (13)
Systemic	0 (0)

POT: periocular topotecan; IVC: intravenous chemotherapy. #1 eye with regressed vitreous seeds was enucleated for a persistent large tumor

achieve complete remission of seeds, one eye (2%) required external beam radiotherapy, and five eyes (13%) required enucleation. The management was decided based on the status of the other eye, response to IVC of the main tumor and hope for vision salvage. Eighteen eyes (47%) had recurrent vitreous seeds which were treated with POT alone in 5 eyes (28%), reinitiation of IVC with POT in 4 eyes (22%), intravitreal topotecan in 8 eyes (44%), and enucleation in 1 eye (5%). At a mean follow-up period of 8.5 months (median 7 months; range 1–15 months), 19 eyes (95%) with focal vitreous seeds and 12 eyes (68%) with diffuse vitreous seeds could be salvaged. None of our patients developed extraocular tumor extension or systemic metastasis.

Discussion

Vitreous seeds can arise either from a budding large endophytic tumor spontaneously or as a result of chemotherapy-induced tumor necrosis.[5] In both cases, the systemic chemotherapeutic drug fails to attain adequate concentration in a relatively avascular vitreous, leading to persistent seeds despite regression of the main tumor.[4] Subconjunctival or subtenon's injection is a safer and an efficient route of drug delivery of chemotherapeutic agent, with the resulting vitreous concentration higher than that achieved by systemic chemotherapy alone.[9,10,14-16,19] In a report on the response of vitreous seeds to high-dose chemotherapy coupled with periocular carboplatin, the authors observed that 95% eyes belonging to ICRB group C, 85% of group D, and 57.5% of group E eyes could be salvaged.[20] The authors concluded that intensive management with primary high-dose chemotherapy and concurrent periocular route of chemotherapy with carboplatin provides gratifying outcome in retinoblastoma with vitreous seeds.[20] Shields *et al*. suggest the use of periocular chemotherapy in advanced bilateral group D and E eyes to boost the local chemotherapy dose in localized

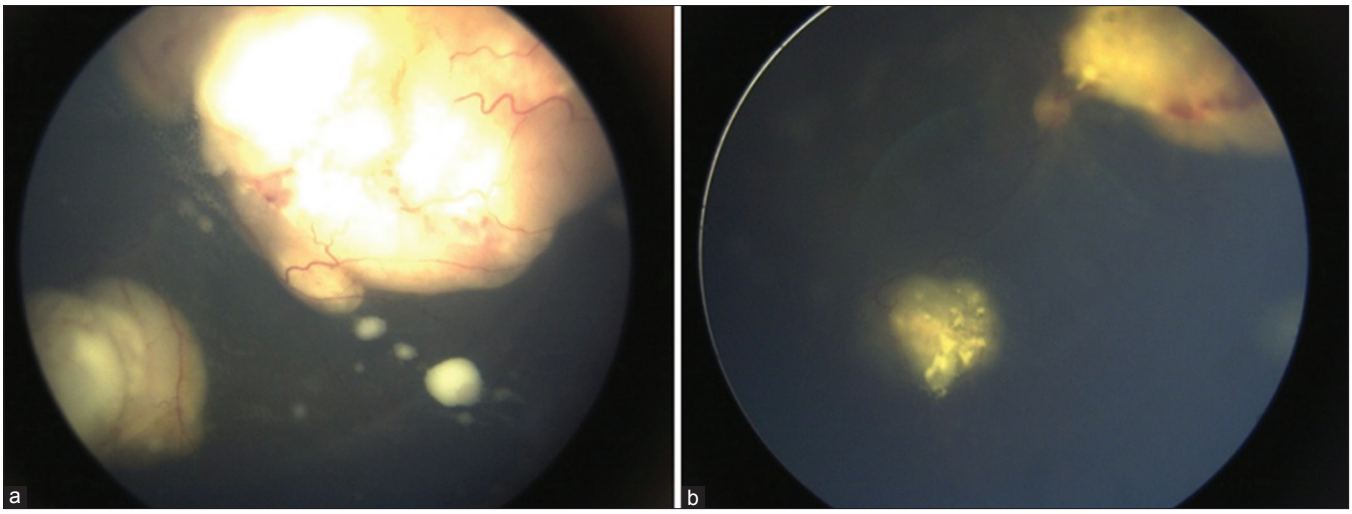

Figure 1: (a) Left eye of a 11-month-old male with group C retinoblastoma with focal vitreous seeds. (b) Complete regression of the vitreous seeds following 2 doses of periocular topotecan (POT) with concurrent intravenous chemotherapy (IVC) given at 4 weeks interval which was maintained at 15-month follow-up

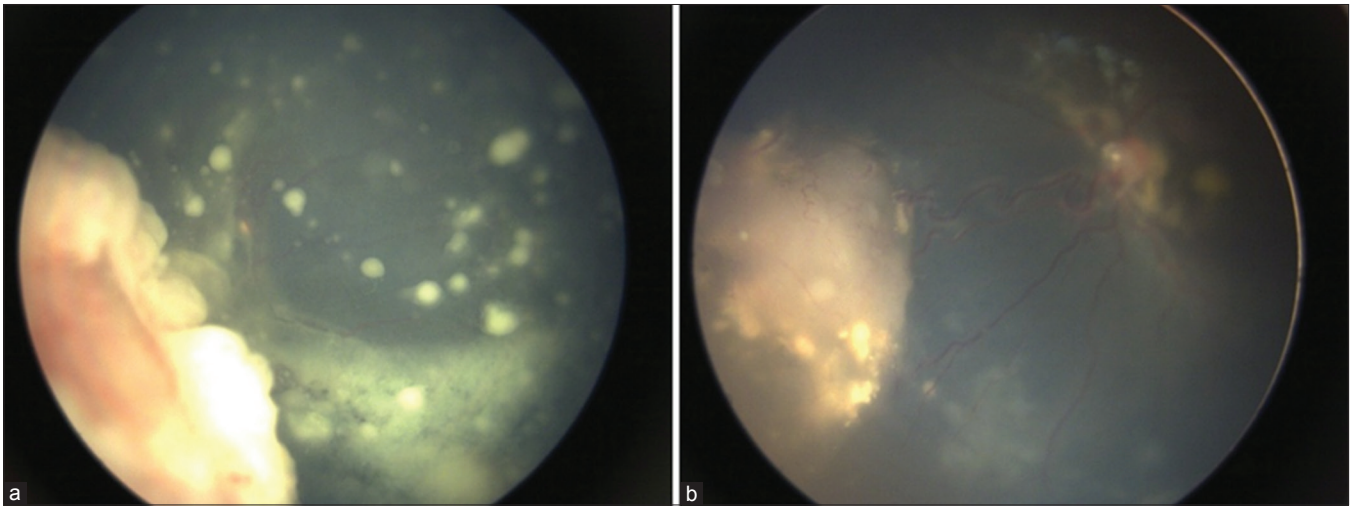

Figure 2: (a) Right eye of a 2-year-old female with group D retinoblastoma with diffuse vitreous seeds. (b) Total resolution of vitreous seeds following 3 doses of POT with concurrent IVC given at 4 weeks interval which was maintained at 11-month follow-up

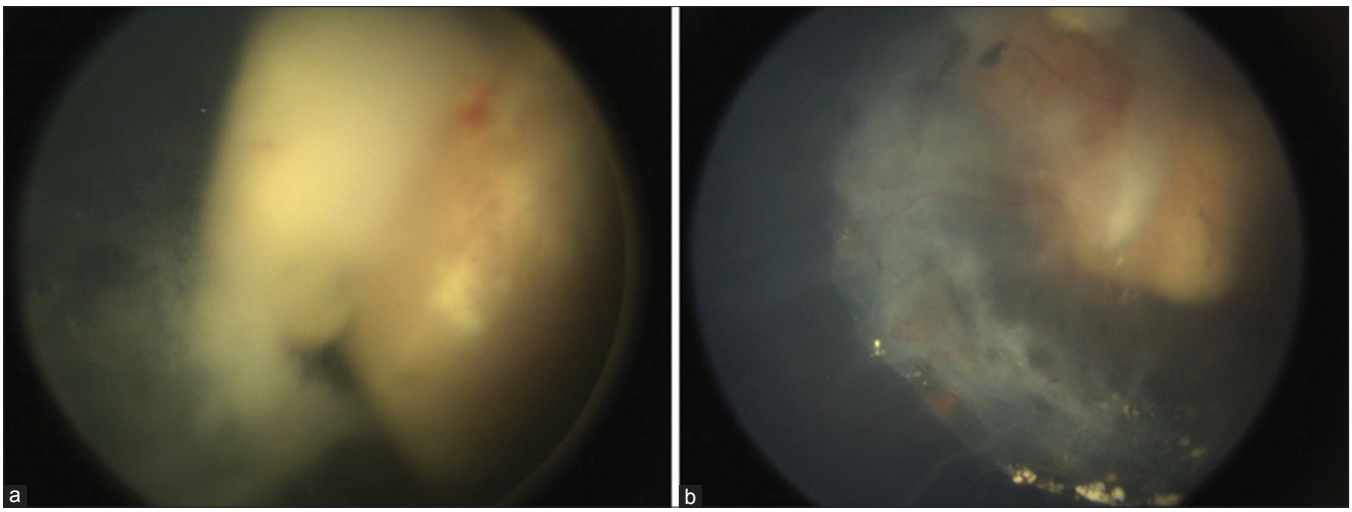

Figure 3: (a) Vitreous cloud overlying a large tumor in group E retinoblastoma in a 16-month-old female. (b) Partially disappearance of the vitreous cloud with non-viable vitreous seeds after 5 doses of POT with concurrent IVC given at 4 weeks interval (IVC extended to 9 cycles in the patient to achieve maximum tumor volume reduction). The vitreous seed regression was maintained at 9-month follow-up

recurrences.[9] Among the chemotherapeutic drugs, topotecan has been found to have an excellent trans-scleral penetration and increased stability with time without any sight-threatening complications.[15,16,19]

Topotecan is a semi-synthetic derivative of camptothecin, a pentacyclic alkaloid from the Chinese yew tree, *Camptotheca acuminate*.[21] It exerts its cytotoxic effect predominantly in S-phase because of its selective topoisomerase-I-inhibiting effect.[21] The use of topotecan has been described in various cancers including cervical cancers, small-cell lung carcinoma, and pediatric tumors such as neuroblastoma and rhabdomyosarcoma.[14] In 2004, Chantada *et al.* were the first to prove the efficacy of topotecan in retinoblastoma when they achieved tumor regression by intravenous topotecan in nine patients with extraocular and refractory intraocular retinoblasotoma.[22] Brennan *et al.* also studied the efficacy of topotecan-based therapy on 27 patients with bilateral advanced intraocular retinoblastoma.[23] Their protocol included two cycles of topotecan and vincristine, followed by two cycles of carboplatin and vincristine, and finally one cycle of topotecan plus vincristine.[23] With this, they obtained an eye salvage rate of 74.3% for ICRB group C to E eyes. Adverse effects including neutropenia (10%) and thrombocytopenia (15%) were noted which were transient.[23]

Shields *et al*. in a report on 40 consecutive eyes with viable vitreous seeds that received a combination of intravitreal melphalan (20–30 μg) and topotecan (20 μg) found that it can provide a long-term tumor control.[2] Rao *et al*. achieved complete regression of vitreous seeds in 17 of 17 eyes (100%) with 3-weekly intravitreal topotecan and concluded that topotecan is effective and safe in controlling focal and diffuse refractory vitreous seeds in retinoblastoma.[18] Additionally, the authors noted no adverse effects of intravitreal topotecan both locally and systemically.[18] Intra-arterial delivery of topotecan has also been successful with an eye salvage in 55% of patients who received three cycles of toptecan with melphalan.[24] In yet another study on 10 eyes with active retinoblastoma who received a mean of 3.8 intra-arterial injection of topotecan and melphalan, the authors found complete regression of the main tumor in 90% and partial regression in 10% of the patients.[25]

The use of POT was first reported by Carcaboso *et al*. in 2007 in rabbit models and the authors noted a significant level of topotecan in the vitreous due to its favored passage through blood–retinal barrier.[19] In their comparative study of topotecan by periocular and intravenous route in rabbits, the authors detected a comparable vitreous level of topotecan, thus initiating the idea of periocular route to avoid systemic complications.[19] A study to determine the maximum tolerated dose of POT by Chantada *et al*. led to the conclusion that 2 mg could be safely given 2 weeks apart with minimal adverse effects.[14]

Periocular chemotherapy can present with certain adverse effects including eyelid edema, ecchymosis, orbital fat atrophy, extraocular muscle fibrosis leading to strabismus, and optic atrophy.[9,11] However, these complications have been mostly observed with carboplatin.[9,11] Mulvihill *et al*. reported motility restriction in all 12 eyes that received periocular carboplatin, and they concluded that the use of periocular carboplatin must be limited and only in specific indications.[11] The authors also reported technically difficult enucleation procedures with a higher risk of globe rupture due to the presence of extensive orbital soft tissue adhesions.[11] This is in contrast to the six cases in this study where the authors did not encounter orbital adhesions on enucleation, making the dissection technically easier and safer. POT injections caused eyelid edema and conjunctival chemosis in seven (18%) of our patients, which have also been noted in previous studies.[14,15,19,26] However, these effects were transient and treated with systemic and local anti-inflammatory medications. Despite a report on serious drug reaction that was noted on intravenous carboplatin and topotecan given together, the authors did not encounter a similar effect in any of the 35 patients.[27] Carcaboso *et al*. and Tsui *et al*. have tested methods of POT delivery using episcleral implant and mixing topotecan with fibrin sealant, respectively, to produce a sustained periocular reservoir of the drug to extend the duration of intraocular drug penetration and to minimize local toxic effects.[17,28]

In conclusion, POT is an effective drug for the management of vitreous seeds in retinoblastoma. POT for vitreous seeds can be safely given in patients undergoing triple drug chemotherapy with vincristine, etoposide, and carboplatin without any local and systemic adverse effects.

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Conflicts of interest

There are no conflicts of interest.

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