Commentary: Periocular topotecan for retinoblastoma

We have long surpassed the era when enucleation or external beam radiotherapy (EBRT) was the only option for managing eyes with advanced retinoblastoma. Despite the groundbreaking advancements over the past few decades in the field of retinoblastoma management, persistant/recurrent vitreous seeds continue to remain the nemesis of ocular oncologists all over the world.

Shield *et al.* reported that intravenous chemotherapy could salvage only 30% of eyes with diffuse vitreous seeds.[1] The relative resistance of vitreous seeds to systemic chemotherapy can be attributed to the avascularity of vitreous humor and has always been an impetus for exploring additional and alternate methods of more effective drug delivery into the vitreous. Wilson *et al.* found that cryotherapy increases the access of systemic chemotherapy into the vitreous.[2] Pascual Pasto *et al.* studied rabbit eyes and found that inhibition of blood–retinal barrier by systemic pantoprazole can lead to increased delivery of chemotherapy into vitreous.[3]

The acceptance of intravitreal chemotherapy as a safe method of drug delivery was a quantam leap in the attempts to control the vitreous seeds.[4] Shields *et al.* achieved 100% vitreous seed control and 88% globe salvage over 3-year follow-up using intravitreal melphalan and/or topotecan. Employing enhanced safety techniques including choosing the correct site for injection in a region of least or no seeding, triple freeze–thaw cryotherapy at the needle site on withdrawal, and 1 min of constant ocular irrigation, they did not note any case of extraocular extension during 192 injections.[4] Combining intra-arterial chemotherapy with intravitreal chemotherapy has further improved globe salvage in eyes with advanced retinoblastoma.[5] Despite all the precautions, there is always a risk of extraocular tumor spread from intravitreal while injecting an eye with active tumor due to spillover, reflux, or tumor growth along the needle track.[6] Development of endophthalmitis after intravitreal injection in an eye with retinoblastoma, especially in developing countries, is, needless to say, a dreaded complication.

Periocular chemotherapy is a relatively safer technique in this regard, as the chemotherapeutic drug is injected into the subtenon's space, thus avoiding any breach in the ocular integrity. Periocular carboplatin has been used in conjunction with systemic chemotherapy for retinoblastoma over two decades. Carcaboso *et al.* found considerable vitreous levels of topotecan in rabbit eyes after periocular delivery, as a consequence of a favored passage across the blood–retinal barrier.[7] Up to 2 mg periocular topotecan (POT) is considered safe and can be an effective alternative to intravitreal

chemotherapy for controlling vitreous seeds.[8] Various modalities of periocular drug delivery have been explored by various authors including episcleral implants, fibrin sealants, and nanomolecular composition. Though periocular chemotherapy entails a risk of optic atrophy and muscle fibrosis, which can lead to strabismus and render enucleation rather difficult, these complications are seen mostly with periocular carboplatin. Periorbital topotecan is associated with mild and transient side effects such as eyelid edema and chemosis.

The efficacy of POT in tumor regression has been reported previously. In an article in the current issue of IJO, Sthapit *et al.* have studied the efficacy of POT along with systemic chemotherapy in managing focal and diffuse vitreous seeds. The author could achieve remission of vitreous seeds (VS) in 63% of eyes and eye salvage in 95% of eyes with focal vitreous seeds and 68% of eyes with diffuse seeds.[9] The complications associated with POT were mild and transient and no metastasis was noted.

In our opinion, POT is a safer alternative to intravitreal chemotherapy, especially in eyes with diffuse VS where finding a safe sight for injection is challenging. POT achieves good VS control with minimal complications. The results so far have been promising and there is a need for larger studies with longer follow-up to corroborate the results.

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