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Guest Editorial

# Intravitreal chemotherapy (IVitC): An adjuvant eye salvage modality

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## 1. Introduction

Tumour control of vitreous seeds remains the biggest challenge in managing retinoblastoma due to the lack of vasculature in the vitreous.[1,2] Subretinal and vitreous seeds have a poor response to laser photocoagulation and intravenous and intra-arterial chemotherapy. Previously vitreous seeds were managed with plaque brachytherapy, external beam radiation therapy, or enucleation.[2,3] Intravitreal chemotherapy (IVitC) has increased the global salvage rate and changed retinoblastoma management, specifically in patients with associated vitreous seeds.[4] Intravitreal chemotherapy is a safe and effective eye preservation treatment modality in eyes with persistent or recurrent vitreous seeds. It is used as an adjuvant after standard intravenous or intra- arterial chemotherapy.[2–5] Currently, IVitC has shown excellent outcomes with globe salvage in RB with vitreous seeds.[6,7]

## 2. Types of Vitreous Seeds

The classification of vitreous seeds depends on the distribution in the globe, distance from the retinal surface, and pattern. According to distribution, vitreous seeding is classified into focal (one quadrant) and diffuse (seeds in more than one quadrant of the eye globe) vitreous seeds. Based on the distance from the retinal tumour surface, vitreous seeds are categorized as either less than or more than 3mm from the retina's surface. Based on the pattern, three subtypes are identified: Type I (dust-like seeds), Type II (sphere-like seeds), and Type III (clouds-like seeds).

The response of vitreous seeds to the IVitC can be categorized into four types: Regression Type 0 (Total disappearance of the vitreous seeds), Type I (refringent or calcific vitreous seeds), and Type II (amorphous, nonspherical, inactive residual vitreous seeds); or (d) a combination of the last two (regression type III).[6,8]

## 3. Injection Technique

The injection is given 3-3.5 mm away from the limbus via the pars plana approach, and the 30-gauge needle points towards the centre of the vitreous cavity. The globe is rotated after injection for the uniform distribution of the drug. Following injection, the needle is withdrawn through the first ice ball of the cryotherapy procedure, which prevents needle track seeding, and triple freeze-thaw cryotherapy should be applied at the injection site.[6,9–11] Sterility was maintained during the procedure, and no vitreous seeds, subretinal fluid or tumour scars were present up to hours at the injection site.[4,10,11]

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## 4. Preparation of Drugs

Melphalan or topotecan is the most extensively used agent, and it can be used alone or combined. Commercially Melphalan is available as 50 mg lyophilized powder. At first, the powder is mixed with 10 ml of 0.9% sodium chloride solution, a concentration of 5 mg/ml of Melphalan is prepared, followed by vigorous shaking of the drug till the solution becomes clear. Then 1 ml of diluted (5 mg/ml) Melphalan is mixed with 24 ml 0.9% sodium chloride to prepare 0.2 mg/ml (200 $\mu$g/ml) Melphalan solution. The dosage of IVitC Melphalan is adjusted and customized according to the age, like 20 $\mu$g/0.10 ml for 0–12 months of age, 25 $\mu$g/0.125 ml for 1–3 years of age, and 30 $\mu$g/0.15 ml for three years and above. After reconstitution of Melphalan, it is better to use it within 2 hours.[12]

## 5. Discussion

Munier et al. reported that complete remission with regression of vitreous seeds and retention of the globe was achieved in 87% (20/23) eyes in a median follow-up period of 22 months (9-31 months). All the cases had already been previously treated with IVC or IAC. Intravitreal Melphalan was given in a dose of 20-30 $\mu$g/0.1 ml, depending on globe size. The IVitC can be administered every 7-10 days till complete regression of vitreous seeding is achieved.[7]

Shields et al. studied 11 eyes with recurrent vitreous seeds after intravenous chemotherapy. They found complete regression of control vitreous seeds and globe salvage in 100% of eyes using intravitreal injection of 20-30 $\mu$g melphalan at a 2-year follow-up.[9]

Ghassemi and Schields explored low doses of Melphalan with eight $\mu$g/0.1 ml to highest doses of 50$\mu$g/0.1 ml. Eyes treated with low-dose Melphalan (8-10 $\mu$g) showed poor control and little or no ocular toxicity. Those treated with the highest dose (30-50 $\mu$g) showed excellent control but caused ocular toxicity. They reported intravitreal Melphalan in a dose of 20-30 $\mu$g/0.1ml appears to be ideal.[13]

A study showed that melphalan IVitC with a standard dose of 20-30 $\mu$g/0.1 ml is an effective and relatively safe eye salvage treatment modality for retinoblastomas. Complete regression with no active seeds by a median number of 4 IVitC injections (range 3-8) was achieved in 78% (21/27) eyes. Complete regression (type 0) was seen in 14 (52%) eyes, calcific seeds (type I) in 8(30%) eyes, and amorphous seeds (type II) in 5 (19%) eyes. Among 27 eyes with Retinoblastoma (RB), 6 (28.7%) were in group C, and 21 (71.3%) were in group D. 83% (5/6) eyes with group C RB, and 76% (16/21) eyes in group D RB showed a complete response (p = 1.0). A complete response was noticed in 64% (7/11) eyes with persistent vitreous seeds and in 88% (14/16) eyes with recurrent vitreous seeds (p = 0.37). The vitreous seeds were successfully controlled in 82% of eyes with active subretinal seeds by IVitC. All (100%) eyes with focal vitreous seeds were controlled compared to 65% of diffuse vitreous seeds by IVitC (p = 0.04). IVitC (Melphalan) avoided enucleation and radiation therapy.[14]

Vitreous seeds are classified as dust (23.1%), sphere (61.5%), and cloud (15.4%). IVitC melphalan of 30-40 $\mu$g in 1 or 2 injections was proved effective treatment in 69.2% of eyes with regression of vitreous seeds.[15,16] Dust seeds respond more rapidly than spheres, while clouds need more injections to regress.[17,18]

Ghassemi et al. observed the outcome of intravitreal topotecan (8–20 $\mu$g in 0.04 mL of balanced salt solution) combined with Melphalan (40 $\mu$g in 0.04 mL of diluent) in nine eyes and achieved complete regression of vitreous seeds in all 9 eyes following a mean of 1.9 injections. They explored 66% eye salvage with no recurrence of the tumour and vitreous seeds at 15 months follow-up, and the combination drug therapy to be safe and effective. Three patients (33%) underwent enucleation because of tumour recurrence and persistent anterior chamber lesions.[11] Kiratli et al. also showed better combined intravitreal Melphalan and topotecan results for avoiding enucleation and rapid control of vitreous and subretinal seeds.[19] Rao et al. reported on 100% vitreous seed control in patients using a mean of three intravitreal topotecan as monotherapy of 30 mg/0.15 ml. They showed topotecan is very safe and limited toxic effects.[10]

Kivela et al. found success with intravitreal methotrexate injection (400 $\mu$g) but considered 20-27 times injections into the eye of a child for one year compared to Melphalan with 4-6 injections over 2-3 months.[20]

Significant ocular complications following IVitC are uncommon, and careful injection procedures and standard dosing regimens are helping to reduce the risk and complications and avoid irreversible vision loss. Ocular side effects may occur in patients after standard Melphalan IVitC.[14,21]

Brodie et al. reported that a dosage of 20–30 $\mu$g of melphalan injection could not affect the retinal function of photopic ERG.[22] Whereas Francis et al. have reported on reduced ERG amplitude, indicating permanent retinal toxicity.[23]

## 6. Ocular Toxicities and Complications

Retinal toxicity was categorized into five grades: Grade I: <2 clock hours of salt-and-pepper retinopathy in the peripheral retina and anterior to or at the equator; Grade II: >2 clock hours of retinopathy that extends anteriorly or at the level of the equator; Grade III: retinopathy that extends posterior to the equator but not involving the macula; Grade IV: retinopathy involving the macula (maculopathy); and Grade V: extensive pan retinopathy with concomitant optic disc atrophy.[24]

Complications included temporary hypotonia of 2 weeks or less, temporary epithelial defect, vitreous haemorrhage[11], salt-and-pepper retinopathy[7], and transient localized vitreous haemorrhage[7,13], transient hypotony, retinal haemorrhage, endophthalmitis, retinal detachment, cataract, phthisis bulbi[9,13]. The enucleation rate was 11% in eyes that received combination drugs (Melphalan and topotecan) compared to 62% enucleation that received Melphalan alone.[16] Eyes treated with low-dose Melphalan (8-10 $\mu$g) showed poor control and little or no ocular toxicity. Those treated with the highest dose (30-50 $\mu$g) showed excellent control but caused ocular toxicity.[13] They reported intravitreal Melphalan in a dose of 20-30 $\mu$g/0.1ml appears to be ideal.[13] No documented complications were observed after intravitreal melphalan injection.[25]

## 7. Conclusion

Intravitreal chemotherapy is an effective adjuvant treatment modality to treat the retinoblastoma with vitreous seeds and helps salvage the globe. Melphalan is the most used drug, and a dose of 20-30 $\mu$g/0.1 ml is effective modality for controlling vitreous seeds with limited toxic side effects. Topotecan may be used as monotherapy or combined therapy with Melphalan. The combination modality (Melphalan and Topotecan) reported fewer toxicities.

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## 10. Conflict of Interest

None.

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