

Ocular Oncology Update

Intravitreal chemotherapy for vitreous seeding in retinoblastoma Recent advances and perspectives

Francis L. Munier, MD^{a,b,*}; Marie-Claire Gaillard, MD^a; Aubin Balmer, MD^a; Maja Beck-Popovic, MD^c

Abstract

For decades intravitreal chemotherapy (IVIc) remained virtually banished from the therapeutic armamentarium against retinoblastoma, except as a heroic attempt of salvage before enucleation in only eyes with refractory vitreous seeding. Very recently, we have initiated a reappraisal of this route of administration by (1) profiling eligibility criteria, (2) describing a safety-enhanced injection procedure, (3) adjusting the tumoricidal dose of melphalan, and (4) reporting an unprecedented efficacy in terms of tumor control of vitreous seeding. Since then, intravitreal chemotherapy is being progressively implemented worldwide with great success, but still awaits formal validation by the ongoing prospective phase II clinical trial. As far as preliminary results are concerned, IVIc appears to achieve complete vitreous response in 100% of the 35 newly recruited patients irrespective of the previous treatment regimen, including external beam radiotherapy and/or intra-arterial melphalan. In other words, vitreous seeding, still considered as the major cause of primary and secondary enucleation, can now be controlled by IVIc. However, sterilization of vitreous seeding does not necessarily translate into eye survival, unless the retinal source of the seeds receives concomitant therapy. In conclusion, IVIc, an unsophisticated and cost-effective treatment, is about to revolutionize the eye survival prognosis of vitreous disease in advanced retinoblastoma.

Keywords: Intravitreal chemotherapy, Melphalan, Retinoblastoma, Vitreous seeding

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Introduction

Despite tremendous advances in the conservative management of advanced retinoblastoma, the major cause of failure remains the persistence or recurrence of resistant vitreous seeding. Vitreous seeds result from the clonal selection of retinoblastoma cells that are able to proliferate in the avascular vitreous environment. Cells surviving in such hypoxic conditions are prone to develop chemo-resistance properties

beyond all classic therapeutic modalities. Pharmacokinetic studies have recently shown that, if the novel routes of administration such as peri-ocular and intra-arterial chemotherapy have greatly improved the ocular penetration of the drugs compared to systemic chemotherapy, the achieved vitreous concentration is barely tumoricidal, and does not last long enough for tumor control. One way to deliver the desired vitreous drug concentration would be to perform intravitreal chemotherapy. However, as with any invasive procedure,

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^a Unit of Pediatric Ocular Oncology, Jules-Gonin Eye Hospital, University of Lausanne, Lausanne, Switzerland

^b Institute for Research in Ophthalmology (IRO), Sion, Switzerland

^c Unit of Pediatric Hematology-Oncology, University Hospital CHUV, Lausanne, Switzerland

* Corresponding author. Address: Head Retinoblastoma Clinics, Head Oculogenetics Unit, Jules Gonin Eye Hospital, 15 Av. de France, CH-1004 Lausanne, Switzerland. Tel.: +41 21 626 85 80.

e-mail address: Francis.Munier@fa2.ch (F.L. Munier).

intravitreal chemotherapy has been proscribed in the management of retinoblastoma, due to the risk of loco-regional and systemic tumor spread.

Conditional rehabilitation of intravitreal chemotherapy

In the light of these data, we have decided to revisit the feasibility of injecting the chemotherapeutic agent directly into the vitreous cavity through the pars plana as the best way to achieve the appropriate drug concentration. As a first step we have tested the value of ultrasonic bio-microscopic (UBM) imaging of the anterior segment, using a 35 MHz transducer, to predict the safety of a pars plana route of administration. This allowed us to show that tumoral contamination of the posterior chamber can be assessed by UBM with high sensibility and specificity even in the absence of anterior chamber involvement.¹ Our next step was to profile the safety of intravitreal injections for retinoblastoma by parametrizing all risk factors for tumor spread and by designing an injection technique minimizing the addressed risks.² These preliminary studies paved the way to the first report on efficacy of intravitreal chemotherapy for vitreous disease in retinoblastoma as an alternative to enucleation or external beam radiotherapy.³

Here below we describe the state of the art procedure for intravitreal chemotherapy including diagnosis considerations, prevention of tumor spread, technical issues and monitoring of the response to treatment.

Diagnosis considerations

IViC should not be performed unless a) the tumoral nature of the seeding is unequivocal and differentiated from other mimicking conditions, such as old vitreous hemorrhage or vitritis, b) the tumoral viability of the seeding is obvious, which can sometimes require an observation period to document the vitreous growth. Finally the retinal source of the seeding must be identified and, if still active, must be concomitantly eradicated.

Prevention of tumor spread

The underlying mechanisms leading to tumor spread can be classified into two categories, passive per-operative and active post-operative. Passive per-operative tumor spread may occur due to the spilling of tumor cells adherent to surgical instruments when removed from the eye, or to the

reflux of contaminated humors secondary to variations of intraocular pressure. Active post-operative exteriorization may occur via tumor growth along a contaminated surgical wound, or in consequence to co-localization of the entry site with a parietal tumor. To be effective in preventing extra-ocular tumor spread, the injection procedure should minimize both active and passive mechanisms of exteriorization.

Concerning the prevention of active mechanisms of exteriorization, UBM-based contra-indications to IViC were identified (Fig. 1). IViC was considered a threat for survival, and thus an absolute contra-indication, in the case of parietal tumor or seeding co-localizing with the entry site, especially if the posterior chamber is invaded. IViC was considered as a threat for eye survival, and thus a relative contra-indication, in the case of anterior hyaloid or retinal detachment at the meridian of the entry site. The risk here is to convert a) vitreous seeding to anterior segment seeding through the perforated hyaloid, or b) exudative retinal detachment to the rhegmatogenous form. This is also the reason why we excluded other injection routes of administration other than the pars plana, such as the trans-corneal approach. Specifically, the technique of injection through the peripheral cornea and iris root not only creates perforation of the cornea but also perforation of the iris and anterior hyaloid. If the first can be secured by cryotherapy, the risk of contamination remains for the latter two, the worst being the creation of a communication between the vitreous cavity and the posterior chamber. The danger is real since anyone who has performed intravitreal injections knows that vitreous incarceration through the sclera can happen while retracting the needle.

The second level of tumor spread prevention is aimed at addressing all risk factors linked to the per-operative passive mechanisms of exteriorization, i.e. the gradient of pressure across the sclera, the size and number of surgical entries, and the duration of surgery. This led us to develop a safety-enhanced injection technique², consisting of an anti-reflux technique and sterilization of the needle tract. Specifically, we first create a transient hypotony by an anterior chamber paracentesis, aspirating the same volume as the one to be injected into the vitreous. The injection itself is performed using a 32G needle, lasts no more than 15 seconds and is followed by a triple freeze and thaw cryo-application to sterilize the pars plana entry site.

Technique of injection

An anterior chamber paracentesis is performed before melphalan injection. A volume of 0.1–0.15 ml (according to

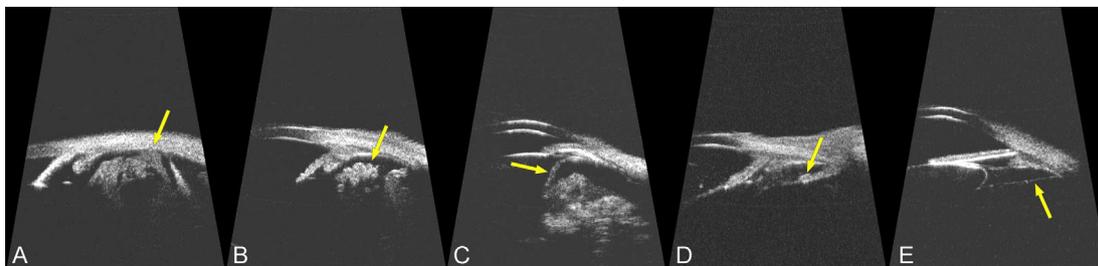


Figure 1. Exclusion UBM criteria: tumor (A), vitreous seeds (B), or retinal detachment (C) at the entry site, as well as invasion of the anterior and posterior chamber (D), or anterior hyaloid detachment (E).

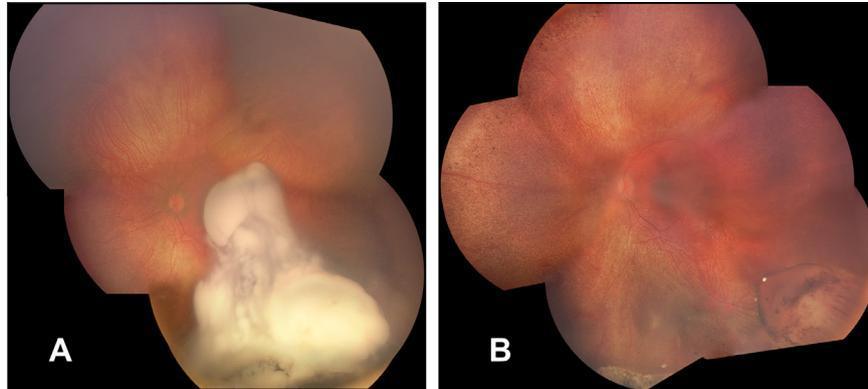


Figure 2. Fundus montage at presentation (A) and at treatment completion (B) 7 months later.

the calculated volume to be injected) of aqueous fluid is aspirated and sent for cytopathologic analysis. A 32G needle mounted on a tuberculin syringe is then introduced perpendicularly 2.5–3.5 mm from the limbus at the desired meridian opposite the seeds through the conjunctiva and sclera under microscope viewing until the needle tip reaches the center of the vitreous cavity. The injected dose is 20 μg in most cases but can be cumulatively increased by 2–4 μg up to 30 μg for each of the following situations: (1) age over 2 years; (2) diffuse nature and/or high density of the seeding; (3) previous intra-arterial exposure to melphalan and (4) relapse after previous IViC. Upon removal of the needle three cycles of freeze and thaw cryoapplications are given at the injection site. The eye is then carefully shaken with a forceps in all directions to enable even distribution of the drug.

Follow-up and response monitoring

At each visit the residual vitreous tumor burden is reassessed and IViC carried out every 7–10 days, up to eight injections if a response can be documented, until complete seed fragmentation is observed or complete response is achieved (Fig. 2). Complete response is established if the seeds (1) completely disappear (vitreous seeding regression type 0), or convert into (2) refringent and/or calcified residues (vitreous seeding regression type I), (3) amorphous often non-spherical inactive residues (vitreous seeding regression type II), or (4) a combination of the latter two (vitreous seeding regression type III). An injection of consolidation is usually given once a complete response is observed. IViC can be repeated if vitreous recurrence occurs from another source.

Unprecedented tumor control of vitreous seeding

We reported the first case series showing the efficacy and safety of intravitreal chemotherapy (IViC) in retinoblastoma patients presenting with vitreous disease.³ Twenty-three consecutive heavily pretreated patients presenting vitreous seeding and eligible for IViC were included in this retrospective non-comparative study. The study population consisted of 18 bilaterally affected patients, 10 of whom had only one eye, and five patients with unilateral retinoblastoma. IViC was proposed as an alternative to external beam irradiation or enucleation for recurrent (74%) or refractory (26%) seeds. Almost 2/3 of this population received intra-arterial melphalan chemotherapy before IViC. Overall, success with control

of vitreous seeds was achieved in 21 of 23 eyes (91%) after a mean number of four injections. Globe retention was achieved in 87% of cases with only 2 eyes enucleated for progressive disease and one for phthisis bulbi unrelated to IViC. All retained eyes were in complete remission, and there were no cases of orbital or systemic retinoblastoma recurrence over a mean 22 months' follow-up. The Kaplan–Meier estimate of ocular survival rates at 2 years was 84.14% (95% CI 62.48–95.28%). All patients were alive without evidence of extraocular spread (95% CI 82.19–100%). We have now extended the follow-up of this initial cohort of 20 conserved eyes with a mean tumor-free eye survival (unpublished data) of 32 months (17–42 months).

Retinal toxicity appeared to be limited to the site of injection in the form of a peripheral well demarcated salt-and-pepper retinopathy in 10 eyes (43%). In fact, this local toxicity confined to the site of a higher concentration of melphalan along the needle passage serves to increase the security level of the procedure. There was no ophthalmoscopic or fluoroangiographic evidence of retinal toxicity at other locations. Similarly, we failed to detect any optic coherence tomography (OCT) changes within the macula after IViC (unpublished data). A transient localized vitreous hemorrhage in two eyes (8.5%) was the only ocular complication observed. Specifically, IViC was not found to cause corneal endothelium insufficiency, cataract (one case was radiation-induced), uveitis, endophthalmitis, or retinal detachment.

For the first time the eye retention rate of the worst retinoblastoma eye group (group D and all cases with recurrent or refractory vitreous seeding) appeared to parallel that of groups A–C without external beam radiotherapy.

Conclusions and perspectives

Although IViC appears to offer a safe and efficient salvage option, its validation awaits the results of a prospective phase II clinical trial. Special attention will be paid to long term safety and retinal toxicity assessed by electroretinogram, fluorescein angiography and OCT. In a preliminary report we have shown that photopic ERG amplitudes were unchanged compared with those recorded prior to the intravitreal injection treatments.⁴

In order to prospectively investigate the role of IViC in the management of vitreous disease, we have launched a phase II clinical trial SPOG-RB-2011 (EudraCT number 2013-002006-31) in collaboration with other centers. Basically, this protocol

is proposing three treatments modalities of *in situ* chemotherapy for recurrent/resistant retinoblastoma according to exclusive inclusion criteria, namely intra-arterial melphalan chemotherapy, peri-ocular topotecan, and intravitreal injection of melphalan.

Specifically, the indication for intravitreal chemotherapy is considered in this protocol when the relapsed tumor burden is mostly vitreal, with or without subretinal seeds, provided that its source is accessible to focal treatment.

If validated, IViC will not only be useful as salvage treatment for recurrent or resistant vitreous seeds, but also as a prophylactic measure in cases of iatrogenic seeding after photocoagulation and plaque surgery, or for group B eyes with ruptured internal limiting membrane (as assessed by fluorescein angiography), i.e. presumptive submicroscopic infraclinical vitreous disease at presentation. In addition, confirmation of IViC safety will pave the way for the development and trials with novel, possibly customized molecules.

Finally, we want to emphasize that although IViC does not replace standard treatment care for groups C and D eyes, we expect that the addition of front-line IViC to state of the art treatment in eligible groups C and D eyes may significantly reduce the exposure to systemic chemotherapy, as well as the indications for enucleation and/or EBR.

Conflict of interest

The authors declared that there is no conflict of interest.

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