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CLINICAL CASE REPORT

Persistence of retinal function after intravitreal melphalan injection for retinoblastoma

Scott E. Brodie · Francis L. Munier · Jasmine H. Francis · Brian Marr · Y. Pierre Gobin · David H. Abramson

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Abstract
Background The risk/benefit profile of intravitreal melphalan injection for treatment of active vitreous seeds in retinoblastoma remains uncertain. We report clinical and electroretinography results after 6 months of one patient who has shown a favorable initial clinical response to intravitreal melphalan injections for treatment of refractory vitreous seeds.
Methods Clinical case report.
Patient The patient presented at age 17 months with bilateral retinoblastoma [OD: International Classification (ICRB) group E, Reese-Ellsworth (R-E) class Vb; OS: ICRB D, R-E Vb] with no known prior family history. The right eye was enucleated primarily. The patient received systemic chemotherapy and extensive local treatment to the left eye. Ten months later, she presented with recurrent disease, including fine, diffuse vitreous seeds. Tumor control was established with intra-arterial chemotherapy and local treatment. Subsequent recurrence was treated with further intra-arterial chemotherapy, local treatment, and plaque radiotherapy with iodine-125. Persistent free-floating spherical vitreous seeds were treated with 4 cycles of intravitreal melphalan injection via the pars plana, with doses of 30, 30, 30, and 20 μg.
Results After 6 months of follow-up, the left eye remained free of active tumor. Visual acuity was 20/40. Photopic ERGs amplitudes were unchanged compared with those recorded prior to the intravitreal injection treatments.
Conclusions Intravitreal melphalan injection for refractory spherical vitreous seeds of retinoblastoma with favorable tumor response is compatible with good central visual acuity and preservation of retinal function as indicated by photopic ERG recordings.

S. E. Brodie · J. H. Francis · B. Marr · Y. P. Gobin · D. H. Abramson
Department of Ophthalmic Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

S. E. Brodie (✉)
Department of Ophthalmology, Mount Sinai School of Medicine, New York, NY, USA
e-mail: scott.brodie@mssm.edu

F. L. Munier
Department of Pediatric Ocular Oncology, Jules-Gonin Eye Hospital, University of Lausanne, Lausanne, Switzerland

B. Marr · D. H. Abramson
Weill-Cornell Medical College, New York, NY, USA

Y. P. Gobin
Department of Interventional Radiology, New York Presbyterian, Weill Cornell Medical Center, New York, NY, USA

Introduction

Treatment for vitreous seeds in patients with retinoblastoma remains unsatisfactory. Seeds are frequently resistant to brachytherapy or traditional forms of chemotherapy and are beyond the reach of local

ablation by cryotherapy or thermal ablation with transpupillary laser. Intra-arterial chemotherapy has been a significant advance, particularly in cases where vitreous seeding takes the form of "tumor dust"—myriad particles of viable tumor cells which form clouds of debris floating freely in the vitreous compartment. These frequently calcify after intra-arterial treatment and, with time, are often gradually absorbed [1].

Spherical globules of viable tumor have often proved more problematic. They are unreachable with cryotherapy or thermal laser, and have frequently proved refractory to repeated cycles of intra-arterial chemotherapy, but may ultimately implant and begin active tumor growth even after months or years of quiescence in the vitreous.

These recalcitrant tumors may be ideal candidates for direct intravitreal injection of chemotherapy. This technique has had a controversial history. Ophthalmic oncologists have long been reluctant to breech the natural encapsulation of the tumor afforded by the intact globe [2].

Recently, interest in intravitreal injections of chemotherapy for retinoblastoma has been revived, perhaps stimulated by the vast experience of ophthalmologists in recent years with intravitreal injections of anti-VEGF agents for treatment of retinal vascular disorders (though reports of reflux of liquid through the injection needle track and demonstration of incarceration of formed vitreous in the needle track in over 40 % of injections might suggest caution) [3, 4].

Furthermore, initial reports of intravitreal melphalan injection into the eyes of rabbits and humans have suggested a significant potential for acute retinal toxicity as monitored by ERG minutes after intravitreal administration of the drug [5, 6]. We have not observed late deterioration of retinal function after successful intra-arterial chemotherapy for retinoblastoma, with follow-up approaching as long as 5 years.

The effectiveness of intravitreal chemotherapy for retinoblastoma has also been unclear. In a recent report of 6 eyes treated with intravitreal methotrexate for relapse (including one with vitreous seeds) after chemoreduction with systemic chemotherapy, an "objective response" was seen in 5 of 6 eyes, but tumor recurred frequently, and two eyes were enucleated [7]. In another report of two cases treated with intravitreal carboplatin injected through a bleb of subconjunctival carboplatin, both eyes required enucleation shortly thereafter due to persistence of vitreous seeds, though the needle tracks were "not patent" and no orbital or remote seeding was noted with 3-year follow-up [8].

Munier recently described the safety profile of his experience with 135 intravitreal injections of 30 eyes. His antireflux method included anterior chamber paracentesis to reduce intraocular pressure prior to the injection and sterilization of the needle track with a triple freeze–thaw technique. With mean follow-up of 13.5 months, no extraocular spread was noted, and, in the five eyes which were enucleated, no tumor cells were seen at the entry sites [9]. Subsequently, his group reported their initial clinical experience with intravitreal injections of melphalan in 23 eyes of 23 patients with active vitreous seeding. With follow-up of 9–31 months, 87 % of globes have been retained, and no extraocular spread of tumor has occurred [10]. They conclude "Although [intravitreal chemotherapy] 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 retinal toxicity assessed by electroretinogram, fluorescein angiography and optic coherence tomography."

One of our patients has recently received intravitreal injections of melphalan for refractory vitreous seeds. We here report this initial experience, including electroretinographic evidence of preservation of retinal function after intravitreal treatment.

ERG recordings were obtained at baseline and at subsequent examinations under anesthesia as described previously [11]. Briefly, ERGs were obtained using a hand-held ganzfeld stimulator and ERG-jet contact lens electrodes, according to a modified protocol based on ISCEV (International Society for Clinical Electrophysiology of Vision) standards [12]. Single-flash light-adapted 3.0 ERG (3.0 cd s/m^2 flash on a 30 cd/m^2 background) responses were elicited and then averaged together in groups of 10. Light-adapted 3.0 flicker ERG responses (3.0 cd s/m^2 flashes at a rate of 30 Hz on a 30 cd/m^2 background) were obtained in bursts of 250 ms, and then averaged together in groups of 10. Replicate examples of the averaged waveforms are shown. Dark adaptation lasted 5 min (in contrast to the 20-min ISCEV standard) as dictated by the need to minimize the total duration of general anesthesia. Dark-adapted 0.01 and 3.0 ERG responses (0.01 or 3.0 cd s/m^2 flashes on a dark background, and red flashes scotopically balanced to the 0.01 cd s/m^2 flashes, a

non-standard stimulus) were obtained from each eye. Dark-adapted 3.0 responses and oscillatory potentials were recorded simultaneously.

In many cases, the dark-adapted recordings were omitted, as photopic and scotopic responses in our retinoblastoma patients have been highly correlated, and the dark-adapted responses have not added sufficient clinical information to justify the necessary prolongation of general anesthesia. B-wave implicit times obtained during these recordings are typically prolonged by the effects of the sevoflurane anesthetic agent. As this effect varies unpredictably, due to the variations in the level of anesthesia, we are unable to analyze the effects of chemotherapy on the ERG-implicit times.

Report of case

A 17-month-old girl presented with bilateral retinoblastoma (OD: ICRB group E, R-E Vb; OS: ICRB group D, R-E Vb.). The right eye was enucleated primarily. The patient then underwent six cycles of intravenous chemoreduction therapy, with vincristine, etoposide, and carboplatin. Local treatment included periocular carboplatin injections, and focal treatment by TTT laser and cryotherapy as indicated. Ten months later, tumor recurred, with regrowth of the original tumor mass as well as diffuse fine vitreous seeds (Fig. 1). A complete light-adapted and dark-adapted ERG study at this time [11] showed essentially intact retinal function (Fig. 2, Column 2).

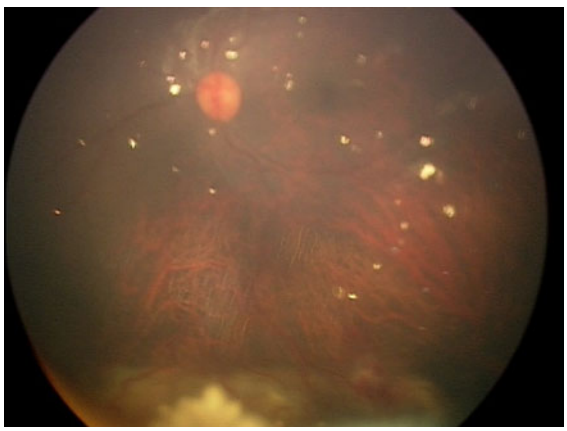

Fig. 1 Fundus appearance of the left eye as of the first recurrence. Note active tumor inferiorly, and scattered vitreous seeds

The eye was treated with 5 cycles of intra-arterial chemotherapy with melphalan and topotecan, as well as focal cryotherapy, with Type I regression of the main tumor mass (Fig. 3). Follow-up ERG after the first treatment cycle was essentially unchanged (Fig. 2, Column 3).

After an initially favorable response, tumor recurred at the border of the main inferior tumor mass, with additional formation of spheroidal vitreous seeds (Fig. 4). Local control of the inferior tumor mass was achieved with intra-arterial chemotherapy (melphalan, topotecan, and methotrexate), focal laser and cryotherapy, and irradiation via application of a radioactive iodine-125 plaque, but free-floating spheroidal tumor masses persisted in the vitreous cavity (Fig. 5). Following this extensive treatment regimen, ERG amplitudes were somewhat reduced (Fig. 2, Column 4).

The patient then underwent 4 cycles of treatment with intravitreal injections of melphalan (doses were 30, 30, 30, and 20 μg) using a 32-g needle via the pars plana. Treatment was carried out according to the protocol of Munier et al. [9, 10], including induction of transient hypotony by anterior chamber paracentesis, and sterilization of the needle track with triple freeze–thaw cryotherapy. As of 6 months of follow-up after the final intravitreal injection, no active tumor was seen (Fig. 6). Visual acuity was 20/40. Comparison of photopic ERG recordings obtained just prior to the initial intravitreal injection with recordings obtained at the 6-month follow-up examination showed essentially complete preservation of the ERG amplitudes (Fig. 2, Columns 4 and 5).

Discussion

We report a favorable initial clinical outcome and substantial preservation of retinal function (as monitored by ERG) following 4 cycles of intravitreal chemotherapy for refractory intravitreal spheroidal tumor seeds. The macula in this child's only retained eye remained free of active tumor, and central fixation was preserved, with visual acuity of 20/40.

The ERGs recorded after the initial recurrence were essentially normal under our recording conditions during examination under anesthesia. The waveforms

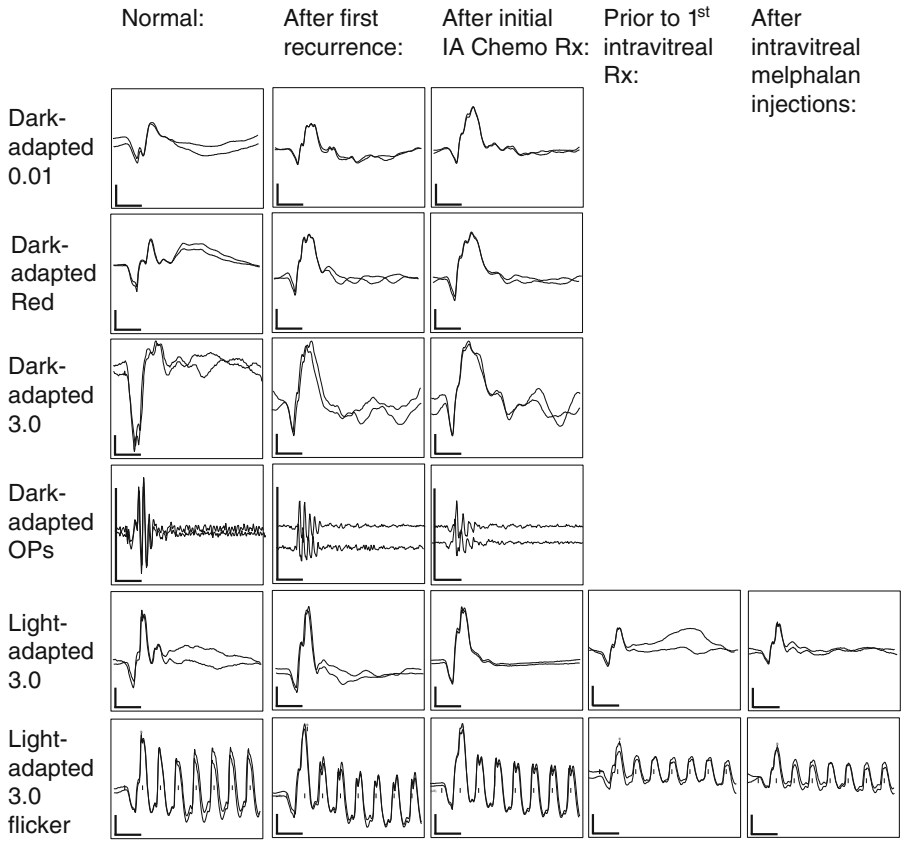

Fig. 2 Ganzfeld ERG responses of the left eye obtained during examination under anesthesia. Recordings conform to ISCEV standards, except that dark adaptation was reduced to 5 min in order to minimize total anesthesia time. Dark-adapted recordings were omitted on some occasions. Tracings are, from *top* to *bottom*: dark-adapted 0.01 ERG; dark-adapted red (a non-standard stimulus) ERG; dark-adapted 3.0 ERG; dark-adapted 3.0 oscillatory potentials (OPs); light-adapted 3.0 ERG; and light-adapted 3.0 flicker at 30 Hz. Columns are as follows, from *left* to *right*: age-matched normal; ERG's after the first recurrence, prior to intra-arterial chemotherapy treatment; ERGs following the initial cycle of intra-arterial chemotherapy; ERGs following extensive treatment of the second recurrence, prior to initial intravitreal melphalan injection; and ERGs following 4 intravitreal melphalan injections. L-shaped scale markers indicate 50 μV (*vertical*) and 50 ms (*horizontal*)

were essentially unchanged after the initial cycle of intra-arterial chemotherapy. After extensive additional treatment, including further intra-arterial chemotherapy, ablations with laser and cryotherapy, and irradiation with an iodine-125 plaque, ERG amplitudes were reduced by about 60 %, to about 60 % of the lower limit of normal, and the ERG waveforms showed some loss of oscillatory detail. These waveform changes are frequently seen in both treated and untreated patients and may be associated with retinal detachment, intraocular inflammation, effects of ablation therapy, drug toxicity, and possibly paraneoplastic effects of viable tumor on the retina. It is not possible at present to sort out the effects of tumor progression and treatment on the ERG waveforms. After successful treatment of persistent vitreous seeds by intravitreal melphalan injection, the ERG waveforms were essentially unchanged (and possibly slightly enhanced) compared with the ERGs obtained immediately prior to this phase of treatment.

It is as yet uncertain that this favorable result will persist, and lengthier follow-up is required. Initially favorable responses to intravitreal chemotherapy injections have previously proven unsustainable in a large fraction of cases [7, 8]. Nevertheless, the persistence of substantial ERG amplitudes following treatment suggests that the doses of intravitreal melphalan used in this case appear to have struck a satisfactory balance between tumoricidal effect and the desire to avoid retinal toxicity.

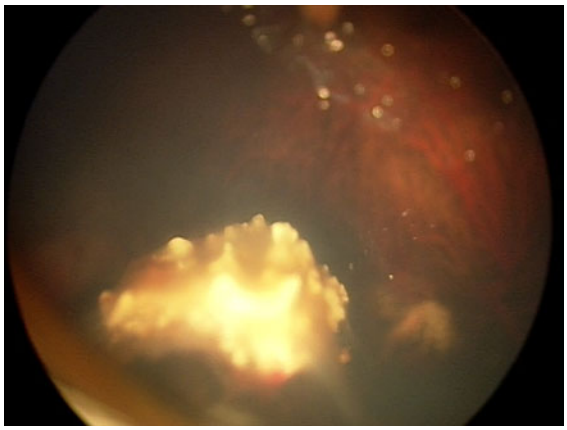

Fig. 3 Fundus appearance after 5 cycles of intra-arterial chemotherapy with melphalan and topotecan and local cryotherapy

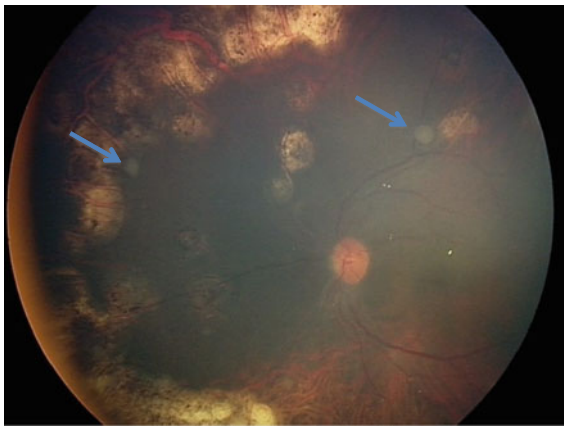

Fig. 5 Fundus appearance after extensive treatment of the second recurrence. Note persistent free-floating spheroidal vitreous seeds (*arrows*)

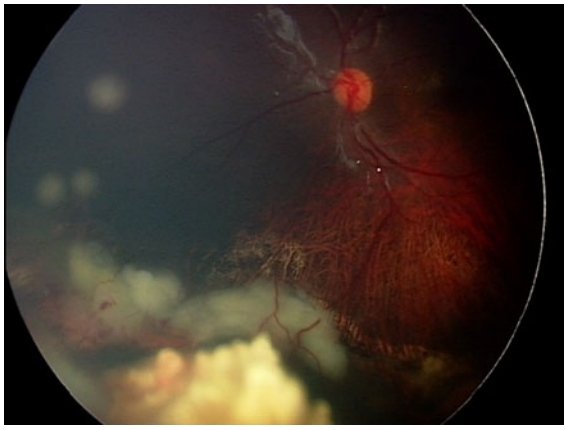

Fig. 4 Fundus appearance at the second recurrence. Note active tumor inferiorly and development of spheroidal vitreous seeds nasally

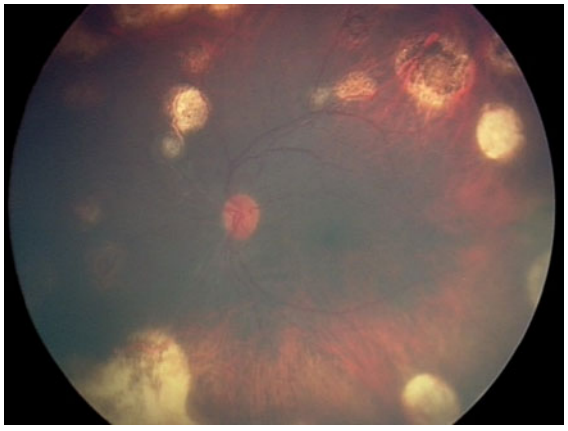

Fig. 6 Fundus appearance 6 months after completion of 4 cycles of treatment with intravitreal injection of melphalan

Conflict of interest None.

Note added in Proof The patient remained free of disease until the 3 month follow-up visit, when recurrence of the main tumor, with shedding of new vitreous seeds was noted. The eye was treated with a ruthenium plaque and received four additional intravitreal melphalan injections without complication. She has subsequently remained without clinically detectable disease, with central visual acuity of 20/50 and photopic flicker ERG amplitude of 42 μV two months after her last treatment.

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