Intravitreal chemotherapy in retinoblastoma: expanded use beyond intravitreal seeds

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The Association for Research in Vision and Ophthalmology, Baltimore, MD, May 2017.

Received 4 February 2018
Revised 9 May 2018
Accepted 12 May 2018
Published Online First 6 June 2018

ABSTRACT

Background/aims Ophthalmic artery chemosurgery (OAC) has changed the face of retinoblastoma treatment and led to a higher rate of globe salvage. The introduction of intravitreal chemotherapy (IVitC) has further enhanced globe salvage with increased success in treatment of intravitreal seeds. Our group has seen success at treating non-vitreous disease that is refractory to OAC using IVitC. This study was undertaken to quantify and report on this success.

Methods A retrospective review was used to identify patients treated with IVitC for indications other than vitreous seeds from two centres. The indication, prior and concurrent treatment, response time and duration of treatment were documented. Kaplan-Meier estimates were used to evaluate ocular and recurrence-free survival. Ocular toxicity was evaluated using the 30 Hz flicker electroretinogram (ERG). Continuous and categorical variables were compared with Student's t-test and χ^2 test, respectively.

Results Fifty-six eyes from 52 retinoblastoma patients were identified. There were no disease-related or treatment-related deaths. One patient developed a second primary malignancy (pinealoblastoma) and subsequent leptomeningeal spread. Ninety-eight per cent of the eyes showed clinical regression. Recurrence was seen in 14.3%. Of the recurrences, five occurred in retinal tumours and three in subretinal seeds. The Kaplan-Meier estimated risk of recurrence in all patients treated was 83.5% (95% CI 7.9 to 14.1) at 10 months. The mean change in ERG over treatment course was −17.7 µV.

Conclusions Intravitreal chemotherapy is successful for the treatment of subretinal seeds and recurrent retinal tumours and could be considered as adjunctive therapy in globe-sparing treatment of retinoblastoma.

INTRODUCTION

The clinical approach to the treatment of retinoblastoma revolves around the first goal of saving life and secondarily preservation of the eye and vision. Accordingly, over the past two decades, a number of approaches aimed to treat retinoblastoma and avoid enucleation have been explored and implemented into practice. For more than 75 years, external beam radiation was the only way to save an eye with vitreous or subretinal seeding. Because of the increased rate of second primary malignancies related to external beam radiation, it was abandoned in favour of intravenous chemotherapy (IVC). Unfortunately, more than half of eyes with subretinal or vitreous seeds treated with IVC require enucleation and, as such, these eyes are often primarily enucleated.[1–3]

Over the past decade, ophthalmic artery chemosurgery (OAC) has greatly changed retinoblastoma treatment.[4–10] With this method, chemotherapeutic agents are administrated directly to the tumour site, achieving their maximum concentration locally. OAC has been used to successfully treat advanced eyes that, in the past, would have been enucleated. Ocular success rates far exceed those of either primary systemic chemotherapy or external beam radiation.[1 5 11] Although the majority of eyes with vitreous seeding can be salvaged with OAC alone, vitreous seeding remains the main reason for enucleation in OAC-treated eyes. With the addition of intravitreal chemotherapy (IVitC), globe salvage is even higher and with shorter time to resolution of active disease.[12–19]

There are limited data on the success of current treatment modalities for subretinal seeds as they are grouped with vitreous seeds in the international classification and are not included at all in the Reese-Ellsworth classification. Seeding of either type (vitreous or subretinal) traditionally holds a very poor prognosis.[11 20 21] In one study, ocular survival in eyes with subretinal seeds only (no vitreous seeds) treated with OAC was 83% in treatment-naïve eyes and only 50% in eyes that had had prior treatment.[22]

To date, IVitC has been used exclusively to control persistent or recurrent vitreous seeding in retinoblastoma that is refractory to systemic intravenous chemotherapy and/or OAC (or in adjuvant treatment with initial OAC). Our group has reported preliminary data, collected from three patients, that showed a novel indication for IVitC for the treatment of persistent or recurrent non-vitreous disease refractory to OAC.[21] Here, we report our expanded experience with IVitC for non-vitreous disease in retinoblastoma.

METHODS

This is a two-centre retrospective chart review, approved by the Institutional Review Boards of Memorial Sloan Kettering Cancer Centre New York, New York, and Xin Hua Hospital Affiliated with Shanghai Jiao Tong University School of Medicine, Shanghai, China, of all eyes treated with intravitreal injections of melphalan and/or topotecan for the management of retinal tumours, subretinal seeds and anterior chamber involvement between November 2013 and February 2017. The study was compliant with the Health Insurance Portability

To cite: Abramson DH, Ji X, Francis JH, *et al*. *Br J Ophthalmol* 2019;**103**:488–493.

and Accountability Act and adhered to the tenets of the Declaration of Helsinki.

Intravitreal injections

Injection of melphalan and/or topotecan were performed as previously described.[17] After induction of anaesthesia, intravitreous melphalan (25–30 µg in 0.05–0.08 mL) was injected using a 30–33-gauge needle, 2–3 mm from the limbus. The injection site was then sealed with cryotherapy before needle withdrawal. Intravitreal topotecan (20 µg in 0.04 mL) was used in patients in whom the sole intravitreal melphalan did not result in the desired response and in whom it was believed that additional treatment was necessary.

Clinical characteristics

Clinical notes and images collected during each examination under anaesthesia by indirect ophthalmoscopy, RetCam fundus photography (Clarity, Pleasanton, California, USA), B-scan ultrasound (OTI Scan 2000; Ophthalmic Technologies, North York, ON, Canada) and ultrasonic biomicroscopy (OTI Scan 2000; Ophthalmic Technologies) were reviewed. Patient data included gender, age at the time of first injection, laterality, tumour classification according to Reese-Ellsworth and International Classification, tumour type (retinal tumour, anterior chamber (AC) tumours or subretinal seeds (SRS)), reason for chemotherapy injection (initial or recurrence) and follow-up time from the beginning of the injection course. Advanced retinoblastoma was defined as Reese-Ellsworth Groups 'Va' or 'Vb' and ICRb (COG Classification) Groups 'D' or 'E'. Treatment data included the number of injections, the time interval between injections, prior treatment, duration of treatment, time to first response noted, concurrent OAC or focal treatment (laser or cryotherapy) defined as occurring within 3 months of the injection.

In all patients, intravitreal chemotherapy was given in cases where patients were not responding to traditional therapy. This was either in sequence with initial treatment or for recurrent disease. Initial treatment was subdivided into two groups: those who were naïve to treatment (initial-naïve) and those who received treatment at an outside hospital but were naïve at our institutions (initial, prior-treated). Both groups received standard treatment until they failed to respond at which point IVitC was added to their regimen. Recurrence was defined as regrowth from a regressed tumour (regression types I–IV) or new SRS after a 3-month interval of no treatment. Persistent disease was defined as a stable, non-calcified tumour that had not grown and was treated at the team's discretion. A tumour was considered new if it grew outside of the ophthalmoscopically regressed tumour.

Outcomes

Outcomes included ocular survival, recurrence-free ocular survival, duration of treatment, time to response and toxicity. Duration of treatment was measured as time from the first injection until the last injection. The time to response was measured as the time from the first injection to that at which regression was first observed. Duration of treatment and time to response was available for 40 eyes. Toxicity was measured by electroretinogram (ERG) recordings obtained during regularly scheduled examinations under anaesthesia as previously described.[23] Pretreatment measurements from the day of the first injection or immediately prior to that were compared with measurements obtained at the visit immediately following the last injection (on average 11 weeks). Thirty-Hertz photopic flicker amplitude data were used and response amplitude changes of >25 μV were considered clinically meaningful.[23] ERG was considered stable if the change was within 25 μV. Improvement was defined in cases

Table 1 Patient characteristics

	All eyes	Subretinal seeds	Retinal tumours	Anterior chamber	P values (SRS vs retinal tumours)
No of eyes	56	27	26	3	
Mean age at first injection (months)	24 (6–89)	16 (7–44)	25.6 (6–68)	50.7 (26–89)	0.063
Sex (female)	27	12	13	66.7	0.67
No of advanced eyes	40	24	14	3	0.004
Indication for treatment					
Initial-naïve	11	6	5	0	0.81
Initial-prior treated	17	8	9	0	0.75
Recurrence	28	13	12	3	0.92
Mean follow-up (months)	15.0 (3–38)	15.4 (3–38)	15.2 (3–34)	9.23 (4–18)	0.89
Mean no of injections	3.29 (1–14)	2.81 (1–9)	3.81 (1–14)	3 (2–4)	0.11
Mean response time (days)	21.0 (5–75) *	22.4 (5–75)†	19.4 (6–62)‡	21 (7–28)	0.18
Mean duration treatment (days)	44.9 (7–125)*	42.7 (14–125)†	47.2 (7–77)‡	55.67 (21–84)	0.23
Prior OAC (%)	82.1	88.9	76.9	66.7	0.26
Prior focal therapy (%)	78.6	70.4	84.6	100	0.22
Prior IVC (%)	37.5	55.6	73.0	33.3	0.19
Concurrent OAC (%)	32.1	33.3	30.8	33.3	0.85
Concurrent focal (%)	75.0	77.8	73.1	66.7	0.70
Recurrences (%)	14.3	11.1	19.2	0	0.45
Mean time to recurrence (months)	5.89 (3.4–10.1)	4.67 (3.4–6.6)	6.63 (4.6–10.1)	NA	

*Duration of treatment and response time taken from 40 eyes only.
†Duration of treatment and response time taken from 21 eyes only.
‡Duration of treatment and response time taken from 19 eyes only.
IVC, intravenous chemotherapy; NA, not applicable; OAC, ophthalmic artery chemosurgery; SRS, subretinal seeds.

Table 2 Tumour classification

Reese-Ellsworth classification (RE)		International classification (ICRb)	
Group	Number of eyes (% of total)	Group	Number of eyes (% of total)
I	3/56 (5.4%)	A	0/56 (0%)
II	4/56 (7.1%)	B	8/56 (14.3%)
III	8/56 (14.3%)	C	2/56 (3.6%)
IV	0/56 (0%)	D	38/56 (67.9%)
V	41/56 (73.2%)	E	8/56 (14.3%)
Total	56	Total	56

where an increment of at least 25 μV was observed, worsening in cases with a decrement of at least 25 μV. ERG amplitudes were classified in six groups as follows: undetectable (less than 0.1 μV), poor (0.1–25 μV), fair (25.1–50 μV), good (50.1–75 μV), very good (75.1–100 μV) and excellent (more than 100 μV).

Biostatistics

Statistical analysis was performed with Prism (GraphPad Software, La Jolla, California, USA).

Kaplan-Meier survival data with the log-rank test were used to estimate the risk of recurrence and the Mantel-Cox test was used to compare survival curves. In all cases, 95% CIs were used. Chi-square test was used to compare categorical variables while Student's t-test was used when continuous categorical variables.

RESULTS

Clinical characterizations of the eyes

Fifty-six eyes from 52 patients with retinoblastoma treated with intravitreal injections of melphalan and/or topotecan for the treatment of non-vitreous disease were analysed. Patient demographics and disease classifications of the treated eyes are reported in tables 1 and 2. Fifty-seven per cent were bilateral and 71% had advanced disease. The mean age at the time of the first injection was 24 months. A total of 140 injections of 30 µg of melphalan were given in 50 eyes while the remaining six eyes received a total of 27 injections of 25 or 30 µg of melphalan and concomitant 23 injections of 20 µg of topotecan. Six eyes required addition of topotecan and this included four with retinal tumours and two with SRS.

The clinical features of the treated eyes are reported in table 1. The eyes are stratified by tumour type: retinal tumours (26/56), anterior chamber involvement (3/56) and subretinal seeds (27/56) (table 1). The mean number of injections across all groups was 3, the mean duration of treatment was 43 days and the mean response time was 23 days. Prior treatment and concurrent treatment are outlined in table 1. Thirty-two per cent of the eyes received concurrent OAC and 82% received prior treatment with OAC (table 1).

The indications for treatment are listed in table 1. There was no significant difference in indication between SRS and retinal tumours. In addition, there was no significant difference between the three groups in tumour type, sex or age. There were significantly more advanced eyes in the subretinal seed group as compared with the retinal tumours. No new tumours or persistent tumours were identified. Overall recurrence occurred with a frequency of 11% and 19% for the SRS and retinal tumours, respectively, with an average time of recurrence of 4.7 and 6.7 months, respectively, with a mean follow-up time of 15 months (table 1).

Clinical response and duration of response

There were no disease-related or treatment-related deaths. One patient developed a second primary malignancy (pineoblastoma) and subsequent leptomeningeal spread. There was one retinal tumour that did not respond to therapy. All other tumours (SRS, anterior chamber involvement and the remaining retinal tumours) responded (figure 1). The mean duration of the treatment was 44.9 days and the mean time to first response was 21 days. There was no significant difference in either the duration of treatment or the response time when comparing groups (table 1). In addition, there was no significant difference in the number of recurrences when comparing concurrent OAC (p=0.59) or concurrent subconjunctival topotecan (p=0.18) with patients who did not receive these therapies.

Electroretinogram

ERG was available for 33 eyes at both pre-IVitC and post-IVitC time points. Figure 2A shows the change in ERG amplitude registered in each eye after the last injection. The mean decline in ERG was −17.7 μV. ERGs declined in 30.3% of patients (by an average of 46 µV), were undetectable before and after treatment in 12.1% of eyes, and remained stable, and detectable in 57.6% of eyes (figure 2B).

Ocular survival

The Kaplan-Meier estimate of overall ocular survival in this cohort was 97.4% at 30 months (95% CI 2.2 to 14.4) (figure 3). There was one enucleation in this cohort at 9 months following initial injection.

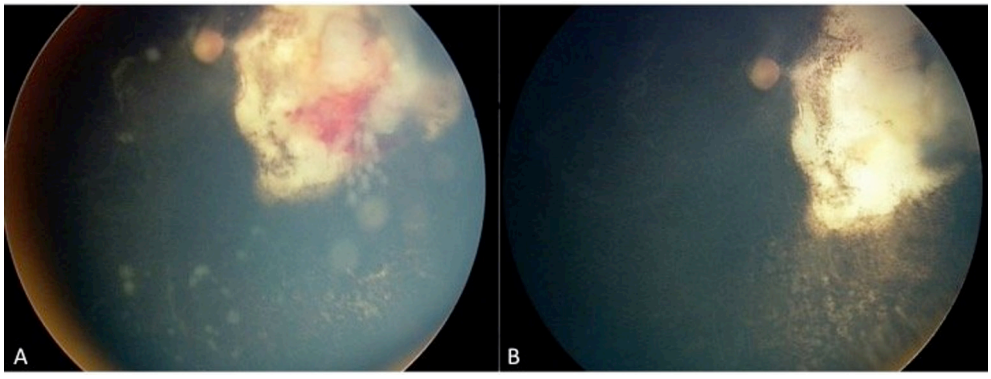


Figure 1 Representative fundus photograph showing response to intravitreal chemotherapy. (A) Before treatment. (B) After treatment.

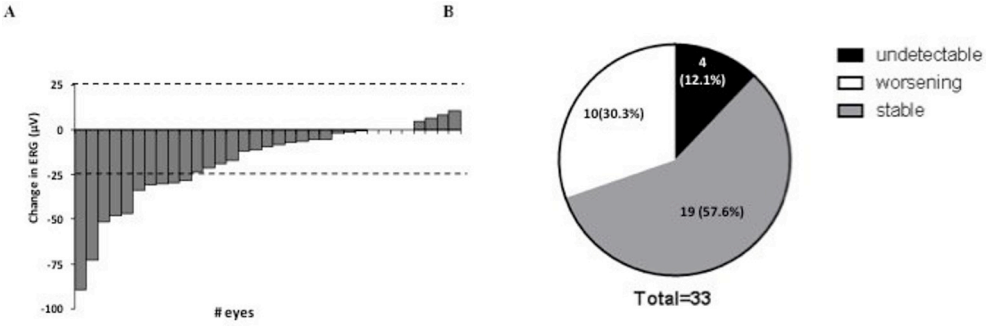


Figure 2 Electroretinogram (ERG) response recorded in 33 eyes treated with Intravitreal injections. (A) Waterfall plot showing the change in ERG amplitude between the initial (baseline) measurement and the follow-up visit after the last injection. (B) ERG change greater than 25 μV or −25 μV was categorised as improvement or worsening, respectively. For ERG values <0.1 μV, eyes were categorised 'undetectable'. Eyes with stable ERG were the eyes for which the ERG change is less than 25 μV.

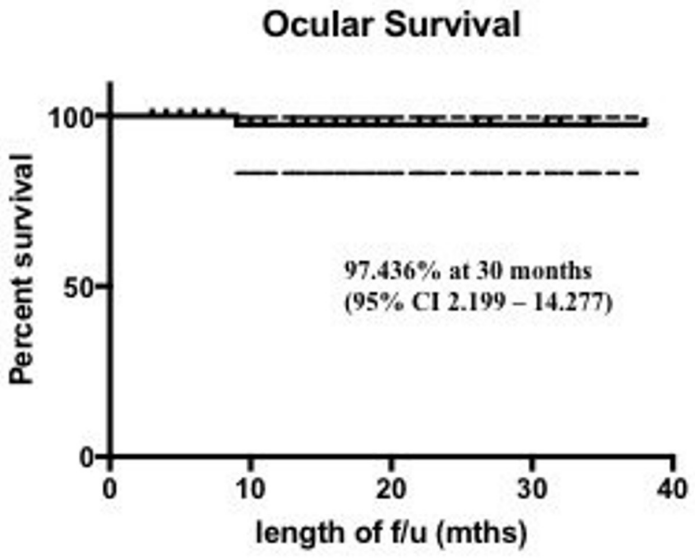
Recurrence-free ocular survival

Tumor type

Recurrence after intravitreal treatment was seen in 8 of the 56 eyes (14.3%). Of the recurrences, five occurred in retinal tumours and three in SRS. Two of the recurrences went on to have OAC while the others were successfully treated with local therapy using a combination of laser, cryotherapy and IVitC. Six of the eight had had prior treatment with IVC and seven had OAC. The Kaplan-Meier estimate of recurrence-free ocular survival in all patients treated was 83.5% (95% CI 7.9 to 14.1) at 10 months (figure 4). The recurrence-free ocular survival is not significantly different between SRS and retinal tumours, 87.6% (95% CI 8.3 to 21.7) and 78.4% (95% CI 12.1 to 21.3) at 10 months, respectively.

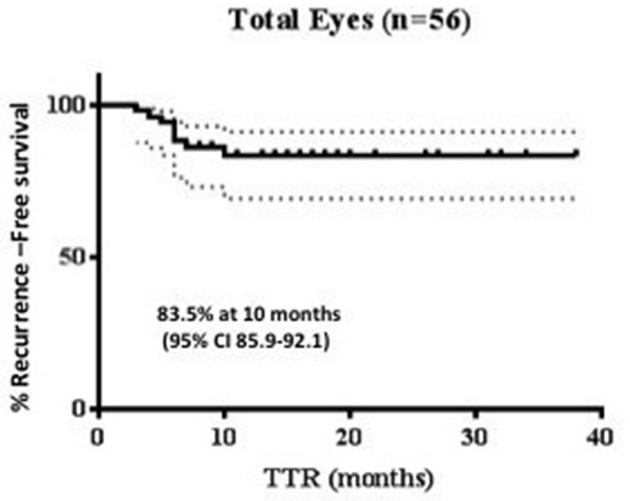
Indication type

The Kaplan-Meier estimates for recurrence-free ocular survival showed no significant difference in initial treated versus those with recurrent disease at 10 months, 74.8% (95% CI 13.3 to 23.3) and 92.2% (95% CI 5.9 to 20.4), respectively. When examining further initial prior-treated and initial-naïve, there was no significant difference between the two groups, 88.9%



Time (mths)	10	20	30
% ocular survival	97.436	97.436	97.436
# at risk	34	14	8

Figure 3 Kaplan-Meier curve for ocular survival Kaplan-Meier estimate of overall ocular survival.



Time (mths)	0	10	20	30
# at risk	56	31	12	8

Figure 4 Kaplan-Meier curves for recurrence free ocular survival
Kaplan-Meier curves showing time to recurrence in all eyes.

(95% CI 9.5 to 45.6) and 63.7% (95% CI 20.1 to 32.0), respectively. The recurrence-free survival was, however, statistically different when comparing initial prior treated and those treated for recurrent disease (p=0.039).

DISCUSSION

In our study, intravitreal chemotherapy was successful at achieving regression for both retinal tumours and SRS 78.4% and 87.6% at 10 months respectively, with a low recurrence rate. Ocular survival was 97.4% at 30 months. Retinoblastoma treatment in developed countries has completely changed in the last decade, first with the advent of OAC and then with the addition of IVitC to overcome the obstacle of vitreous seeds.[24] IVitC has had tremendous success in treating vitreous seeds, and our observation has been that it also has an effect on both retinal tumours and SRS.[21] In the present study, we found that the expanded use of intravitreal chemotherapy was able to achieve a high rate of success. This was true for all three tumour types evaluated and regardless of whether the treatment was initial treatment or treatment for a recurrence.

There was only one patient, in the retinal tumour group, who did not respond. However, this was patient was among our early attempts at IVitC and, as there was no response noted at 7 days, care was quickly escalated to OAC. It is possible that with more time, this patient would have responded, given our mean response time of 23 days. IVC has a recurrence rate of 46% for SRS while intra-arterial chemotherapy has a salvage rate of 50% in previously treated eyes with SRS.[22 25] Our finding that intravitreous chemotherapy has a 12.4% recurrence rate (at 10 months) suggests this new approach may offer higher salvage rates.

There were significantly more advanced eyes in the SRS group, as expected from the classification schemes. Despite this, the Kaplan-Meier estimation of risk of recurrence was not significantly different between the two groups though there was a trend to suggest a higher risk with the retinal tumours.

It has been previously shown in a mouse model that tumour load is significantly reduced with intravitreal injections of melphalan.[26] Melphalan has a known high retinal permeability. In a pharmacokinetic study in rabbit model by Buitrago *et al*, it was shown that there is a high concentration of melphalan in the retina at 15 min after intravitreal injection lasting up to 12 hours postinjection in contrast to the 5 hours that it remains in the vitreous.[27] This correlates with the known retinal toxicity but also may explain the success seen in our study in RS and retinal tumours.

Interestingly, there was a tendency for the initial-prior treated eyes to do worse than the recurrent group and the initial-naïve group. As many of these patients were referred to our centres after inadequate response to prior treatment at an outside institution, the selection of patients within this group may have introduced some inherent bias.

In this cohort, there was one enucleation done for bleeding and phthsis. Pathological examination of this eye revealed no active tumour. There was one second primary malignancy, a pinealoblastoma that ultimately developed leptomeningeal spread and is currently undergoing treatment. Consistent with the known retinal toxicity of intravitreal chemotherapy, there was a significant worsening in the ERG in 30.3% of the eyes.[28]

As previously reported, 11% of advanced eyes primarily treated with OAC have gone on to require enucleation.[12] We have now shown that IVitC is an additional modality that can be used to salvage the eye both primarily and in recurrent cases. Consideration of intravitreal injection in these cases may offer additional options to physicians and families.

Contributors LH, DHA, JHF, FC, SEB, XJ: design, data analysis, writing.

Funding This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748, The Fund for Ophthalmic Knowledge, Inc. and Perry's Promise Fund.

Competing interests None declared.

Patient consent Not required.

Ethics approval IRB.

Provenance and peer review Not commissioned; externally peer reviewed.

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