

Reduction of severe visual loss and complications following intra-arterial chemotherapy (IAC) for refractory retinoblastoma

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Received 5 February 2017

Revised 20 March 2017

Accepted 22 March 2017

ABSTRACT

Background Intra-arterial chemotherapy (IAC) for retinoblastoma has been documented as causing visual loss and ocular motility problems. A lack of safety data has precluded its acceptance in all centres.

Methods Retrospective cohort study of patients with retinoblastoma from 2013 to 2015 who had a healthy foveola and relapsed following systemic chemotherapy. All required IAC. The correlation of complications with doses of melphalan +/- topotecan used and putative catheterisation complications was assessed. Ocular complications were determined using vision, macular (including pattern visual evoked potentials (PVEPs)), retinal electroretinograms (ERGs) and ocular motility functions. Efficacy (tumour control) was also assessed.

Results All eyes had age appropriate doses of melphalan with five having additional doses of topotecan. Severe physiological reactions requiring adrenaline were seen in six patients during the catheterisation procedure. Difficulty was documented in accessing the ophthalmic artery in 7/27 catheterisations. The median/mean number of courses of chemotherapy was three. No child had severe visual loss as assessed by age appropriate tests (median follow-up 20.9 months, range 3.7–35.2 months). One child had nasal choroidal ischaemia and a sixth nerve palsy. Post-IAC PVEPs were performed in eight and reported as normal. All post-IAC ERGs were normal apart from one (total dose 20 mg melphalan 0.8 mg topotecan). Tumour control was achieved in six of nine cases.

Conclusion The proportion of visual and ocular motility complications may be reduced by providing age-adjusted doses of melphalan. Dose rather than complications from catheterisation is the most important risk factor for ocular injury.

INTRODUCTION

There has been a paradigm shift in the management of retinoblastoma with the acceptance of chemotherapy being delivered directly to the ophthalmic artery: intra-arterial chemotherapy (IAC). Many units around the world are using IAC for retinoblastoma¹ but the lack of safety profile data has delayed universal acceptance.^{2–5} Globe salvage without risk of metastases yet with retained vision would be the goal of any treatment strategy for retinoblastoma. Using thorough orthoptist assessments, age appropriate visual testing in combination with visual evoked potentials (VEPs) and electroretinograms (ERGs) on awake children, we have previously

demonstrated that 40% of our earliest cohort developed third nerve palsies⁵ and 42% of eyes with healthy foveolae had severe visual loss after intra-arterial melphalan.⁶ We identified high doses of melphalan, catheterisation complications and previous radiotherapy as potential risk factors for visual loss and were interested in how modification of these factors could ameliorate the complications.

METHODS

This was a retrospective cohort study conducted between January 2013 and December 2015. Eyes with tumours involving the foveola extending to the foveola were excluded. Approval for the use of IAC in this study was obtained from the Great Ormond Street Hospital Children Drugs and Therapeutics Committee and Barts Health Clinical Effectiveness Unit (#6594) within the tenets of the Declaration of Helsinki. Informed consent was obtained from the parents or legal guardians, after discussion of the findings, potential risks and benefits of the procedure. IAC was considered in cases where the tumours failed to respond adequately to previous treatments or there was a new recurrence not amenable to local therapy (laser, cryotherapy or plaque therapy). All patients were assessed by one of the authors (MAR or MSS) and graded according to the International Intraocular Retinoblastoma Classification (IIRC)⁷ and American Joint Committee on Cancer Staging (AJCC).⁸ All patients had received systemic chemotherapy in the form of six cycles of carboplatin, vincristine and etoposide as first-line treatment. Our method of catheterisation of the ophthalmic artery has been previously reported.^{5,6} Adrenaline was given following severe autonomic reactions.⁹ In addition, we assessed the duration of the procedure and compared this with our initial cohort.⁶

We gave age-appropriate doses^{10,11} at the time of treatment. For melphalan, this resulted in 3 mg for infants aged 6–12 months, 4 mg for children aged 1–3 years and 5 mg for children aged above 3 years. For topotecan, doses were consistently 0.3–0.5 mg for children aged below 3 years and 1 mg for one child aged above 3 years. All children had three cycles of IAC spaced at 4 weeks. All patients had an examination under anaesthesia 3 weeks after each treatment. Fundus Fluorescein Angiograms (FFAs) were performed in patients after treatment.

ERGs and VEPs were performed before and after the procedure wherever possible as previously



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To cite: Reddy MA, Naeem Z, Duncan C, et al. *Br J Ophthalmol* Published Online First: [please include Day Month Year]. doi:10.1136/bjophthalmol-2017-310294

described.⁶ Pattern and flash VEPs were recorded according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards¹² from three occipital electrodes; O1, Oz and O2 referred as FpZ. PVEPs (pattern reversal VEPs) were elicited to high-contrast checkerboards. Data from the midline Oz were analysed and reported in this paper.

As part of our protocol, patients had orthoptic examinations before and 3 weeks after each IAC treatment. This included visual acuity (VA) assessment, cover testing at near (1/3 m) and distance (6 m), ocular motility examination, pupillary assessment and investigation of binocular vision. Visual acuities were assessed using Cardiff Cards (fixed choice preferential looking (FCPL)), Keeler Cards (FCPL), Kays picture tests (optotype) and crowded LogMAR, depending on the age of the child. When possible, VA was assessed unocularly, otherwise binocular VA was measured. If quantitative assessment was not possible, qualitative methods were used, that is fixing and following on a target and whether there was a fixation preference.⁶

RESULTS

From January 2013 to December 2015, 23 eyes of 23 patients were treated with IAC in our department. Fourteen patients with tumours involving the foveola were excluded. Table 1 lists the baseline patient and ocular features of the nine eyes from nine patients who were recruited into this study. The median age at the time of the first IAC treatment was 14 months (range 6–125 months). Three children presented with D eyes according to the IIRC⁷ and the other six eyes had less advanced disease (table 1). All patients were alive at last follow-up (median 20.9 months, range 3.7–35.2 months) with no indication of metastases.

Treatment

All children had received six cycles of systemic chemotherapy (carboplatin, etoposide and vincristine) prior to IAC. None had received radiation in the form of plaque or external beam radiation therapy. The indications for treatment included multiple areas of relapse (5% or 55%), solitary relapse (3) and vitreous seeding (1). All children had age-appropriate doses of melphalan: 3 mg in three infants under 12 months of age, 4 mg in four children (aged 1–3 years) and 5 mg in two aged above 3 years. Four children had solely intra-arterial melphalan (3–5 mg) and five had additional topotecan (0.3–1 mg). The median dose of melphalan was 4 mg and the median number of cycles was 3 (range 2–4) as shown in table 2.

Catheter complications

No child suffered from a neurological event following catheterisation. Difficulty was found in 7 of 27 catheterisations. Six of nine patients suffered from a severe autonomic episode. One child (patient 8) had two uneventful injections of melphalan (5 mg) and topotecan (1 mg), yet the third injection into the ophthalmic artery was associated with an autonomic episode (table 2). He subsequently developed a temporary sixth nerve palsy and choroidal ischaemia.

Learning curve

The average length of time for each procedure was 1 hour 52 min (range 1 hour 6 min to 3 hours 8 min). This compares with our initial cohort⁶ of 12 patients where the average duration was 1 hour 32 min (range from 1 hour to 2 hours 20 min).

Table 1 Summary of patient and ocular features

Feature		Number (%)
Age (months)	Mean (median, range)	n=9
At first IAC		31 (14, 6–125)
Laterality of retinoblastoma	Bilateral	5 (55.6)
	Unilateral	4 (44.4)
Affected Fellow eye status	Foveal tumour	1 (11.1)
	Extra-foveal tumour	3 (33.3)
	Enucleated	1 (11.1)
Affected eye status	Previous treatments	
	Cryotherapy	5 (55.6)
	Laser thermotherapy	7 (77.8)
	EBRT	0
	Plaque brachytherapy	0
	Systemic chemotherapy	9 (100)
Indication for IAC	Edge relapse	
	Solitary	3 (33.3)
	Multiple	5 (55.6)
	Vitreous seeding	1 (11.1)
International Intraocular Retinoblastoma Classification at presentation (American Joint Committee on Cancer Staging ⁸)	A (cT1a)	2 (22.2)
	B (cT1b)	2 (22.2)
	C (cT2a)	2 (22.2)
	D (cT2b)	3 (33.3)
	E	0

IAC, intra-arterial chemotherapy.

EBRT, External Beam Radiation Therapy

Outcome

Tumour control was achieved in six eyes (66%) in this group and the other three eyes (33%) eventually went onto enucleation. The three eyes that underwent subsequent enucleation presented with IIRC grades C (1) and D (2) and were assessed for ocular complications of the treatment prior to enucleation. Of the six eyes that avoided enucleation, a partial response was found in two, requiring additional treatment to one of the initial tumours and new tumours, respectively. Two other eyes had post-IAC consolidation laser.

Vision

All nine patients had age appropriate normal vision⁶ (tables 2 and 3) at the last follow-up (median follow-up 20.9 months, range 3.7–35.2 months). The assessment of infants can be difficult. Four children were assessed with FCPL, four with optotypes (Kay pictures) and one was old enough to use crowded LogMAR testing. No child had a deterioration of vision following IAC.

Table 2 Visual outcomes and complications following intraophthalmic artery (IAC) melphalan +/- topotecan for retinoblastoma: dose, complications and results

Patient no. (age in months)	Dose of melphalan (number of IAC treatments)	Dose of topotecan and which treatment	Catheterisation complications	Tumour controlled at last follow-up	Complications	Visual acuity deterioration directly after IAC
1 (6)	3, 3, 3 mg (3)	0.3 mg (1, 2, 3)		Yes	No	No
2 (10)	3, 3, 4 mg (3)	0.3 mg (1, 2, 3)	Autonomic reaction on second injection	Yes	No	No
3 (12)	4, 4, 4 mg (3)	0 mg	Autonomic reaction on second injection	Yes	No	No
4 (24)	4, 4 mg (2)	0 mg	Autonomic reaction on second injection	No	No	No
5 (36)	4, 4, 5 mg (3)	0 mg	Autonomic reaction on second injection	No	No	No
6 (14)	4, 4, 4 mg (3)	0 mg	Initial failed attempt	Yes	Sluggish pupil	No
7 (125)	5, 5, 5, 5 mg (4)	0.4 mg (3, 4)		No	Slight ptosis	No
8 (38)	5, 5, 5 mg (3)	1 mg (1, 2, 3)	Autonomic reaction on third injection	Yes	Yes (nasal choroidal ischaemia and V1th nerve palsy)	No
9 (11)	3, 3, 3 mg (3)	0.5 mg (1, 2, 3)	Autonomic reaction on second injection	Yes	No	No

Although three eventually had enucleations for progressive disease, none lost vision prior to surgery.

Ocular complications

Although no child developed a third nerve palsy, two had a slight ptosis following IAC and one (patient 6) had a sluggish pupil

(with no motility abnormality nor ptosis) at last follow-up. One child developed a sixth nerve with -4 limitation of abduction directly after the third cycle of IAC. The same child also developed nasal choroidal ischaemia. Visual acuity did not deteriorate and at last follow-up, he had vision of LogMAR 0.1 with limitation of abduction of only -0.5. Fundus fluorescein angiograms demonstrated nasal choroidal ischaemia in patient 8 but not in any of the other children. The foveal avascular zone was intact in all children.

Table 3 Visual outcomes, visually evoked potentials (VEP) and electroretinograms (ERG) following intra-arterial chemotherapy (IAC)

Patient (age in months)	Function			
	VA/VEP pre-IAC	VA/VEP post-IAC	ERGs pre-IAC	ERGs post-IAC
1 (6)	Fix and follow VEP: good	LogMar 0.3 FCPL VEP: good	Normal	Normal
2 (10)	LogMAR 0.6 VEP: ND	LogMAR 0.2 FCPL VEP: good	ND	Normal
3 (12)	LogMAR 0.3 VEP: good BEO	LogMAR 0.1 Opto VEP: good	Normal	Normal
4 (24)	LogMAR 0.1 VEP: good	LogMAR 0.2 FCPL VEP: good	Normal	Normal
5 (36)	LogMAR 0.2 VEP: good	LogMAR 0.0 Opto VEP: ND	Normal	Enucleated ND
6 (14)	Not F+F VEP: good BEO	LogMAR 0.8 Opto VEP: good	Normal	Normal
7 (125)	LogMAR 0.36 VEP: good	LogMAR 0.24 VEP: good	Normal	Subtle reduction rod and cone b-waves
8 (38)	LogMAR 0.3 VEP: good	LogMAR 0.1 Opto VEP: good	Normal	Normal
9 (11)	LogMAR 0.6 BEO VEP: good	LogMAR 0.48 BEO FCPL VEP: good	Normal	Normal

FCPL, fixed choice preferential looking; ND, not done; Opto, optotype; VA, visual acuity; BEO, both eyes open

Electrodiagnostic tests

Eight of nine patients had pre-IAC VEPs and ERGs. One child (patient 5) was unable to be tested before the IAC was given. Eight of nine patients had post-IAC VEPs (table 3) demonstrating good vision. Patient 5 showed an improvement in vision as assessed using optotypes. All patients had post-IAC ERGs, and eight of nine patients showed normal values on testing. The only patient with a subtle reduction of cone and rod function had a cumulative dose of 20 mg of melphalan and 0.8 mg of topotecan. The melphalan dose was the highest in this cohort.

DISCUSSION

The use of IAC in eyes with retinoblastoma has gained considerable momentum, with trends away from enucleation to more attempts at eye-conserving therapy. We have reported on our early experience of IAC for refractory tumours, including complications,⁵ visual outcomes⁶ and pathology findings.¹³ This report aims to quantify the amelioration in side effects and improvement in visual outcomes.

Efficacy

There is no direct correlation between dose and complications as not all children who were given high doses of melphalan in our original visual outcome study lost vision⁶: 40% still retained good vision. Titrating the dose that is efficacious yet not associated with complications is difficult. In this work, all patients had doses of melphalan in keeping with Gobin *et al*'s work,¹⁰ but we note that the authors had advised a reduction in dose if systemic chemotherapy had been given prior to treatment. We did not reduce our IAC melphalan dose.

A child with a C eye (patient 7) had multiple vitreous seeds following systemic chemotherapy and would have been treated with intravitreal chemotherapy now rather than IAC in 2013. That child went on to have an enucleation. Two-thirds of patients (six of nine) with refractory retinoblastoma avoided enucleation using lower doses of melphalan (compared with our earlier cohort) and this compares with success rates of 50%–67% that have previously been reported.^{4 10 14} Peterson *et al*¹⁴ only treated Group D eyes and found that 7.5 mg was effective in salvaging the globe in five children (aged 6 months to 7 years). Group D eyes often have poor visual potential and choroidal ischaemia is a valid sacrifice to avoid enucleation. All patients in our cohort had visual potential, and we were keen to avoid iatrogenic visual loss. It is felt that children who have choroidal ischaemia are unlikely to relapse due to the high concentration of drug in the choroidal vascular bed. The only child to have choroidal ischaemia in this cohort was fortunate that the ischaemia was located nasally and therefore did not affect his visual acuity.

Learning curve

A potential cause for the reduction of complications may be attributed to a learning curve. A surrogate for experience that we were able to measure is length of time for the procedure. The first cohort⁶ involved 12 patients from the first 20 who had IAC. The recent cohort was treated after at least 35 patients had undergone treatment. We were surprised to find that the average length of time of the procedure had actually increased over time. As there were complications during catheter insertion in both cohorts, we felt that the learning curve may play a part but is unlikely to be sole cause for the ocular and cranial nerve complications.

Catheter position

We used the small and flexible 1.2F microcatheter (Balt, Montmorency, France Extrusion), either lodged at the ostium or tracked over a wire into the ophthalmic artery proper if ostial stability cannot be achieved. The ophthalmic artery was catheterised in a stable, non-wedged position to ensure antegrade flow of chemotherapy while maintaining angiographic perfusion of the choroid. Injection of chemotherapeutic agents only took place if angiography demonstrated antegrade flow around the catheter and a visible choroidal blush was seen. Many units use larger catheters,^{10 14 15} which are more likely to cause a wedge effect if inserted into the ophthalmic artery.

One patient (patient 8) developed complications following an autonomic reaction,⁹ and it is difficult to state if the reaction caused the complications as five other patients had a reaction without consequence. This is the second case of a sixth nerve palsy¹⁵ to be described in the literature with the first case involving a 4F catheter with 5 mg of melphalan in a 3-year old child.

Toxicity

No child suffered severe visual loss and one child (11%) developed a cranial nerve palsy and choroidal ischaemia. This study provides reassurance to units that may consider using IAC in patients with age appropriate vision. Munier *et al*³ reported final visual acuities but did not report the proportion of eyes starting with good visual potential. We have previously demonstrated that 42% of children suffer severe visual loss.⁶ It is reassuring that with lower doses of IAC melphalan, normal ERGs were noted in nearly all patients. A deterioration of photopic response has been correlated with improved outcomes¹⁶ and a potential

association of 14 mg of melphalan has been associated with ERG deterioration.¹⁷ One child had a subtle ERG deterioration and had a cumulative dose of 20 mg of melphalan pointing to dose as being an important factor. One child had choroidal ischaemia, yet the ERG was normal demonstrating a large area of functioning retina was present.

The innovative approach of age appropriate visual testing in infants and children with retinoblastoma and awake electrodiagnostic studies including VEPs have enabled us to assess a treatment modality and modify risk factors to determine the cause of complications. The necessarily small sample size reflects the patients with normal visual potential. In addition, there is a mixture of melphalan and topotecan given in some patients, and it is reassuring that there was no summative damage to the retina as demonstrated on electrophysiology.

CONCLUSION

It is essential with new treatments to inform families of potential complications and modify iatrogenic risk factors. A recent review² of IAC has emphasised the lack of visual outcome data. By analysing a subset of patients, we have shown that an age-adjusted dose of melphalan is associated with reduced toxicity and excellent salvage rates.

Acknowledgements We are saddened by the recent demise of our colleague Dr Judith Kingston.

Contributors Study concept and design: MAR, MSS, CD. Acquisition, analysis and interpretation of data: All authors. Drafting of manuscript: MAR. Critical revision for important intellectual content: All authors. Study supervision: MAR. MAR had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests None declared.

Patient consent Patients were non-identifiable in this study.

Ethics approval Barts Health Clinical Effectiveness Unit.

Provenance and peer review Not commissioned; externally peer reviewed.

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Br J Ophthalmol published online April 21, 2017

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