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

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Precis: The proportion of visual and ocular motility complications may be reduced by using age adjusted doses of intra-arterial melphalan in children with refractory retinoblastoma.

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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 (ERG) 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 ischemia 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 20mg melphalan 0.8mg topotecan). Tumour control was achieved in 6 of 9 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 retinoblastoma[1] 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 3rd nerve palsies[5] 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 MAR or MSS and graded according to the International Intraocular Retinoblastoma Classification (IIRC)[7] and 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 3mg for 6-12 month olds, 4mg for 1 to 3 year olds and 5 mg above this age. For topotecan, doses were consistently 0.3 to 0.5 mg for under 3 year olds and 1mg for one child over 3. All children had 3 cycles of IAC spaced at 4 weeks. All patients had an examination under anaesthesia three weeks after each treatment. FFAs were performed in patients after treatment.

ERGs and VEPs were performed before and after the procedure wherever possible as previously described[6]. Pattern and flash VEPs were recorded according ISCEV standards[12] from 3 occipital electrodes; O1,Oz and O2 referred to FpZ. PrVEPs (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 three weeks after each IAC treatment. This included Visual Acuity (VA) assessment, cover testing at near (1/3m) and distance (6m), 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 upon the age of the child. When possible VA was assessed uniocularly, otherwise binocular VA was measured. If quantitative assessment was not possible qualitative methods were used, i.e. 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. 14 patients with tumours involving the foveola were excluded. Table 1 lists the baseline patient and ocular features of the 9 eyes from 9 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). 3 children presented with D eyes according to the IIRC[7] and the other 6 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.

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 tumor		1 (11.1%)
	Extra-foveal tumor		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 IAM	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

Treatment

All children had received 6 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: 3mg in 3 infants under 12 months, 4 mg in 4 children (aged 1 to 3) and 5 mg in 2 above 3 years of age. Four children had solely intra-arterial melphalan (3-5 mg) and five had additional topotecan (0.3 to 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.

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

Table 2. Visual outcomes and complications following intra-ophthalmic artery melphalan +/- Topotecan for retinoblastoma: Dose, complications and results.

Catheter complications

No child suffered from a neurological event following catherisation. Difficulty was found in seven of 27 catheterisations. Six of nine patients suffered from a severe autonomic episode. One child (Patient 8) had two uneventful injections of melphalan (5mg) and topotecan (1mg) 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 ischemia.

Learning Curve

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

Outcome

Tumour control was achieved in 6 eyes (66%) in this group and the other 3 eyes (33%) eventually went onto enucleation. The 3 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 6 eyes that avoided enucleation, a partial response was found in 2, 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 vision[6] (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, 4 with Optotypes (Kay pictures) and one was old enough to use crowded LogMAR testing. No child had a deterioration of vision following IAC. Although 3 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 3rd cycle of IAC. The same child also developed nasal choroidal ischemia. 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 ischemia in Patient 8 but not in any of the other children. The foveal avascular zone was intact in all children.

Electrodiagnostic Tests (EDTs)

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 8 of 9 showed normal values on testing. The only patient with a subtle reduction of cone and rod function had a cumulative dose of 20mg of melphalan and 0.8mg of topotecan. The melphalan dose was the highest in this cohort.

Table 3. Visual outcomes, visually evoked potentials (VEP) and electroretinograms (ERG) following IAC.

	FUNCTION			
Patient (age in months)	**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 Log 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

Abbreviations:
ND: not done
BEO: both eyes open, FCPL: Fixed Choice Preferential Looking, Opto: Optotype ,
F+F: Fixing and Following, Good: Pattern reversal VEPs are evident to 50' or smaller checks

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 outcomes[6] and pathology findings[13]. This report aims to quantify the amelioration in side effects and improvement in visual outcomes.

Efficacy

There is not a direct correlation between dose and complications as not all children who were given high doses of melphalan in our original visual outcome study lost vision[6] : 40% still retained good vision. Titrating the dose that is efficacious yet is not associated with complications is difficult. In this work, eight of nine 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 (6 of 9) with refractory retinoblastoma avoided enucleation using lower doses of melphalan (compared to our earlier cohort) and this compares with success rates of 50 to 67% that have previously been reported[4, 10, 14]. Peterson[14] and colleagues only treated Group D eyes and found that 7.5 mg was effective in salvaging the globe in 5 children (ages 6 months to 7 years). Group D eyes often have poor visual potential and choroidal ischemia is a valid sacrifice to avoid enucleation. The patients in our cohort all had visual potential and we were keen to avoid iatrogenic visual loss. It is felt that children who have choroidal ischemia are unlikely to relapse due to the high concentration of drug in the choroidal vascular bed. The only child to have choroidal ischemia in this cohort was fortunate that the ischemia 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 cohort[6] 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 whilst 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 (#8) developed complications following an autonomic reaction[9] and it is difficult to state if the reaction caused the complications as 5 other patients had a reaction without consequence. This is the second case of a sixth nerve palsy[15] to be described in the literature with the first case involving a 4F catheter with 5mg of Melphalan in a 3 year old.

Toxicity

No child suffered severe visual loss and one child (11%) developed a cranial nerve palsy and choroidal ischemia. This study provides reassurance to units that may consider using IAC in patients with age appropriate vision. Munier and colleagues[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 outcomes[16] and a potential association of 14 mg of melphalan has been associated with ERG deterioration[17]. The one child had a subtle ERG deterioration and had a cumulative dose of melphalan of 20mg pointing to dose as being an important factor. One child had choroidal ischemia 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.

CONCLUSIONS

It is essential with new treatments to inform families of potential complications and modify iatrogenic risk factors. A recent review[2] of IAC has emphasized the lack of visual outcome data. By analyzing a subset of patients, we have shown that an age adjusted dose of melphalan is associated with reduced toxicity and excellent salvage rates.

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Study concept and design: Reddy, Sagoo, Duncan

Acquisition, analysis and interpretation of data: All authors

Drafting of manuscript: Reddy

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