Integrated Treatment during the Intravitreal Melphalan Era: Concurrent Intravitreal Melphalan and Systemic Chemoreduction

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Established Facts

- Seeding is a common cause of retinoblastoma relapse.
- Intravitreal melphalan is an effective strategy for treating vitreous seeding.

Novel Insights

- Concurrent systemic chemoreduction and intravitreal melphalan may be a strategy for effective therapy while minimizing the number of examinations under anesthesia required.
- Intravitreal injection of melphalan-associated toxicity and whether there is additional toxicity with this approach require further research.

Keywords

Retinoblastoma · Chemotherapy · Intravitreal injection · Melphalan · Treatment outcomes

Abstract

Background: Intravitreal injection of melphalan (IVM) is safe and effective for the treatment of seeding in retinoblastoma. Current protocols require weekly injections during examination under anesthesia (EUA). To avoid additional anesthesia exposure for these children, IVM was initiated at the EUA concurrent with the 4th cycle of systemic chemoreduction in a series of 6 patients with persistent seeding. **Methods:** A retrospective review was completed to assess treatment response compared to all patients at our center treated with

IVM and systemic chemotherapy. Overall, 6 eyes of 6 patients were included; salvage therapy included systemic chemoreduction with vincristine, etoposide, and carboplatin and IVM for persistent seeding. **Results:** IVM was initiated in all eyes at cycle 4 of their chemotherapy. Success in eradicating vitreous seeds was 100%; overall salvage rate was 67%. Anterior toxicity was observed in 2 out of 6 eyes and posterior toxicity in 4 out of 6 eyes. **Conclusion:** The concurrent chemoreduction and IVM protocol demonstrated a similar efficacy of globe salvage while sparing children additional EUAs. However, the increased rates of observed melphalan-related toxicities for concurrent therapy are concerning. Further clinical experience is necessary to define the best initiation time and dosing schedule for IVM.

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Introduction

Salvage of retinoblastoma eyes has historically been limited by the presence of seeds, which consist of small tumor foci in the vitreous and subretinal space that can result in multiple new tumors, tumor relapse, and subsequent loss of the eye [1–3]. The advent of a safe and efficacious method for delivering intravitreal injection of melphalan (IVM) has revolutionized the current approach for treating seeding in advanced retinoblastoma [4]. Previous reports on the efficacy of intravitreal melphalan demonstrate 100% success in eradicating vitreous seeding and high globe salvage rates of 68–86% on par with rates previously attained with external beam radiation therapy [5–10].

While success rates are encouraging, the exact timing, dosage, and number of injections is still under review. Currently, no “gold standard” of care has been defined for intravitreal chemotherapy in the same way that norms exist for systemic and intra-arterial chemotherapy. One hypothesis is to combine therapy and initiate concurrent IVM with cycles 4–6 of systemic chemotherapy. This approach has the potential benefit of providing synergistic antineoplastic effects against vitreous seeds while decreasing the overall number of examinations under anesthesia (EUA) that these children experience, given that IVM after systemic chemoreduction often requires 3 or more weekly injections [5, 6].

In this case series, we examine the results of 6 patients diagnosed with advanced retinoblastoma with persistent vitreous seeding during chemoreduction who were treated with concurrent IVM injections with the last 3 cycles of systemic chemoreduction. The main outcome measure was event-free globe survival. The secondary objective was to compare the efficacy and toxicity to previous studies wherein IVM was initiated after systemic chemoreduction (e.g., sequential therapy).

Methods

We conducted a retrospective chart review of patients diagnosed with retinoblastoma at the Children’s Hospital Los Angeles (CHLA) from 2014 to 2017. Patients who received concurrent intravitreal melphalan and systemic chemoreduction for persistent seeding were included. The Institutional Review Board approved this study.

The treatment protocol for retinoblastoma at CHLA has previously been published [11, 12]. The injection procedure closely adheres to the protocol outlined by Munier and colleagues [13–15] and previously published [6]. Although a standardized dosage of melphalan has not been fully established due to the relative nov-

elty of the treatment modality, previous publications support the usage of 20–40 µg. After Francis et al.’s [16] report of electroretinogram amplitude decrease after 30 µg of melphalan, IVM dosing was limited to maximally 30 µg; at our center, 25 µg is the most frequently used dose with modifications made for the clinical burden of seeding.

For the concurrent IVM injection protocol, follow-up EUA and injection were performed at 4-week intervals on the same day as administration of systemic chemoreduction. This protocol was utilized for patients with persistently active vitreous seeding diagnosed after 3 cycles of systemic chemotherapy, with patients receiving IVM on the same day as the 4th, 5th, and 6th cycles of chemoreduction. For persistent or recurrent seeding diagnosed after the completion of systemic chemoreduction, another series of weekly injections was performed following the previously described protocol [5, 6]. One patient received 5 total injections within cycles 4–6 of chemotherapy.

Eyes were classified according to the International Intraocular Retinoblastoma Classification (IIRC) System outlined by Linn Murphree [17] and the seeding classification outlined by Munier [14] and Francis et al. [7, 18].

A retrospective chart review was completed to obtain age at diagnosis, gender, laterality, genetic testing status, length of follow-up, dose and number of intravitreal injections, and clinical response to injection.

Results

Demographic and management details of each case are provided in Table 1. Comparisons to the larger previously published cohort, which included 28 eyes receiving systemic chemotherapy and IVM [5], are displayed in Table 2 by seed class [7, 14]. In this group of 28 eyes, 6 eyes demonstrated persistent seeding during systemic chemotherapy. In the current study, all 6 eyes of 6 patients included underwent attempted salvage therapy with concurrent systemic chemoreduction and IVM due to persistent vitreous seeding. A median melphalan dose of 25 µg and a median of 3 injections were required similar to the larger cohort of patients. The mean cumulative dose of melphalan was just over 100 µg in both groups as well. The median age was slightly older in the concurrent therapy group, and the rate of toxicity was greater. Spherical seeding was only seen in the larger cohort, as this type of seed morphology is described primarily in recurrent cases. Two of 6 eyes required additional IVM therapy after the 3 injections given during chemotherapy. 100% of eyes showed complete resolution of seeding; however, all eyes also demonstrated some level of toxicity. Three eyes developed grade 3 retinal toxicity, and 1 eye developed grade 4 retinal toxicity. Two eyes developed both a cataract and iris atrophy. Four of the 6 eyes were salvaged.

Table 1. Patient demographics and results

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age at diagnosis, months	28	28	22	26	24	13
Sex	F	M	F	M	M	F
Eye	OD	OD	OS	OS	OS	OD
Group	D2	D1	D2	D1	D2	C
Laterality	bilateral	unilateral	unilateral	bilateral	unilateral	bilateral
Genetic status	mosaicism 30%	RB1 missense mutation	negative	splice mutation	negative	13q and 16p deletion
Seed type	cloud	cloud	dust	cloud	dust	dust
Cycles with concurrent IVM, <i>n</i>	4–6	4–6	4	4	4–6	4–6
Total injections	10	6	2	1	3	3
Postchemo IVM	7	1	0	0	0	0
Median IVM dose (range), µg	30 (20–30)	25 (20–25)	20 (20)	25 (25)	25 (25)	20 (20)
Toxicity	grade 3 RPE changes	grade 3 RPE changes	mild cataract, iris atrophy	grade 3 RPE changes	hydrated cataract, iris atrophy	grade 4 RPE changes
Seeding response	resolved	resolved	resolved	resolved	resolved	resolved
Salvage	enucleated	yes	enucleated	yes	yes	yes
Reason for enucleation	recurrence involving ON		recurrence involving ON			

OD, right eye; OS, left eye; RB1, retinoblastoma gene; q, long arm; p, short arm; IVM, intravitreal injection of melphalan; RPE, retinal pigment epithelium; ON, optic nerve.

Discussion

This case series reports the outcomes of a small cohort of patients with retinoblastoma at CHLA treated with systemic intravenous chemoreduction and concurrent IVM for persistently active vitreous seeding. Overall, treatment with systemic intravenous chemotherapy, local consolidation, and concurrent IVM resulted in a globe salvage rate of 67% (4 of 6 eyes) at 11.5 months' median follow-up (range 6–29 months). No eyes were enucleated due to progressive vitreous seeding; IVM was 100% successful in treating vitreous seeding and avoidance of external beam radiation therapy.

A previous series examining all eyes treated with IVM for persistent or recurrent vitreous seeding demonstrated a salvage rate of 68% with 100% success of the IVM therapy in eradicating vitreous seeds [5]. The 67% salvage rate of this case series suggests that concurrent chemotherapy and IVM may be a viable treatment option for patients with persistent seeding. However, there did not seem to be an advantage to concurrent IVM when considering globe salvage rates alone.

A clear benefit to this approach is reduced need for multiple weekly examinations under anesthesia at the end of chemoreduction for additional IVM, although 1 of the

cases did require 7 additional injections. All patients in this series received concurrent IVM injections during their already scheduled EUA along with chemotherapy cycles 4–6. Considering the young age of the patients undergoing IVM (median age 25 months, SD 5.6), the reduction of additional anesthesia sessions is an advantage for this patient population [19]. There were no cases of extraocular tumor spread when performing IVM prior to the completion of systemic chemotherapy for advanced retinoblastoma.

Retinal toxicity was determined based on the system delineated by Munier [14] and classified as grade 1–5. In this case series, 3 of 6 eyes developed grade 3 posterior retinal toxicity described as salt-and-pepper retinal pigment epithelial (RPE) changes extending posterior to the equator but sparing the macula. One eye developed grade 4 retinopathy involving the macula. No eye developed grade 5 retinopathy. IVM-related anterior toxicities occurred in 2 of 6 eyes after injection (neither eye had retinal toxicity). In both these eyes, combined cataract and iris atrophy occurred. In comparison, previous data from our center reported grade 3 or higher retinal toxicity and/or anterior segment toxicity, including cataract, focal iris atrophy, and transient anterior segment inflammation developing in about 43% of patients [5, 6]. Our data from

Table 2. Comparison of concurrent intravenous chemotherapy and IVM with results from a prior study of all eyes treated with IVM and intravenous chemotherapy

	Eyes with concurrent intravenous chemotherapy and IVM treated at CHLA				Eyes from a previous study completed at CHLA [5] ^a			
	class I: dust	class II: spheres	class III: clouds	overall	class I: dust	class II: spheres	class III: clouds	overall
Eyes, <i>n</i>	3	0	3	6	15	8	5	28
Injections, <i>n</i>								
Median	3		6	3	3	4	6	3
Mean	2.7		5.7	4.2	2.9	4.5	6	4
Range	2–3		1–10	1–10	1–6	3–8	1–10	1–10
Melphalan dose, µg								
Median	20		25	25	25	25	30	25
Mean	21.9		26.3	24.1	27.7	26.9	29.9	8
Range	20–25		20–30	20–30	20–40	20–40	20–40	20–40
Cumulative melphalan, µg								
Median	60		140	67.5	75	115	195	85
Mean	58.3		149.2	103.8	81	121.3	179.3	113.2
Range	40–75		25–282.5	25–282.5	25–190	60–210	25–282.5	25–282.5
Age at time of injection, months								
Median	24		31	28	16	16	29	21
Mean	22.3		30.3	26.3	20	20	26	17
Range	16–27		29–31	16–31	6–73	9–33	14–31	6–72
% complications/toxicity	(3/3) = 100%		(3/3) = 100%	(6/6) = 100%	(4/15) = 27%	(4/8) = 50%	(4/5) = 80%	(12/28) = 43%
% enucleated	(1/3) = 33%		(1/3) = 33%	(2/6) = 33%	(5/15) = 33%	(2/8) = 25%	(2/5) = 40%	(9/28) = 32%
% enucleated owing to active tumor	(1/3) = 33%		(1/3) = 33%	(2/6) = 33%	(4/15) = 27%	(0/8) = 0%	(2/5) = 40%	(6/28) = 21%
Seeding regression	100%		100%	100%	100%	100%	100%	100%
Ocular survival owing to active tumor	67%		67%	67%	73%	100%	60%	79%
Overall ocular survival	67%		67%	67%	67%	75%	60%	68%
Patients' survival	100%		100%	100%	100%	100%	100%	100%

IVM, intravitreal injection of melphalan; CHLA, Children's Hospital Los Angeles. ^a This study demonstrates outcomes of intravenous chemotherapy with IVM for persistent or recurrent seeds.

this small case series reflect higher rates of toxicity than previously demonstrated by our center, which examined all patients who received IVM with systemic chemoreduction. This increased toxicity could be attributed to the fact that IVM and systemic chemoreduction were administered concurrently to the posterior segment at therapeutic doses. Another possibility includes the advanced presentation of these patients with persistent seeding that did not respond to chemotherapy alone, which necessitated earlier intervention of melphalan and concurrent therapy and, therefore, made them potentially more prone to developing higher rates of toxicity regardless of management.

It is important to note that unlike intra-arterial chemotherapy [20], systemic chemotherapy alone has not been

associated with retinal toxicity [21]. Intravitreal delivery of chemotherapy is not without its own set of side effects, including retinal toxicity as described by Munier [14]. Suzuki et al. [22] reported findings for anterior toxicity, including iris atrophy and dense cataracts, in 8.7% of eyes (23/264) and diffuse chorioretinal atrophy in 0.8% of eyes (2/264). Ghassemi and Shields [23] reported RPE changes, cataracts, and phthisis in 25% of eyes (3/12). Munier et al. [24] described a localized retinal toxicity rate of 43% (10/26 eyes), and Tuncer et al. [8] reported a rate of 39% (2/7) for RPE mottling at the site of injections. A recent study by Kiratli et al. [25] reported vitreous hemorrhage in 18% of injected eyes (7/39) and “widespread” RPE changes in 8% of eyes (3/39). While the grading system proposed by Munier [14] was not used in this (and other)

studies, “widespread” likely indicates at least greater than grade 3. It has been suggested that doses >30 µg may increase toxicity [16], although acute and diffuse toxicity have been described recently by Chao et al. [26] after only 1 low-dose injection and by Aziz et al. [27] at doses lower than 30 µg. Although our study observed a higher rate of retinal toxicity than prior ocular oncology literature, our cohort is small, and, additionally, the variation in the determination of retinal toxicity limits any direct comparison with the clinical grading we utilized as proposed by Munier [14]. While prior studies reported “diffuse” or “widespread” RPE changes, our study reports greater than grade 3 toxicity. Nevertheless, while this new treatment protocol may reduce the frequency of EUAs, the higher rates of toxicity are a potential concern, and further research with a larger cohort of patients is required.

Our report describes a small series of patients treated for advanced retinoblastoma with vitreous seeding who received primary chemotherapy and concurrent IVM injections initiated with cycle 4 of chemotherapy. Our review demonstrates an overall globe salvage rate of 67%, which is comparable to the 68% salvage rate we reported for all patients treated with systemic chemotherapy and intravitreal chemotherapy [5]. More research and clinical experience is necessary to better define the best time to initiate intravitreal injections for vitreous seeding, as well as the optimal number and dosing schedule for IVM. The

strategy of delivering concurrent IVM and systemic chemotherapy has the advantage of sparing children additional EUAs, although there did not appear to be an advantage for improving globe salvage rates in this small series. There was also an increased rate of ocular toxicity; however, the small size of the cohort limits any definitive conclusions. As ocular oncology centers continue to utilize this treatment for seeding, it is important to develop a consensus regarding the optimal way to integrate IVM into current chemotherapy regimens to optimize globe salvage results while minimizing associated toxicities.

Statement of Ethics

The Institutional Review Board approved this study.

Disclosure Statement

The authors declare that there is no conflict of interest. No conflicting relationship exists for any author.

Funding Sources

This study was supported by the Institute for Families, Inc., the Larry and Cecilia Moh Foundation, and Research to Prevent Blindness.

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