Posterior Vitreous Detachment and the Associated Risk of Retinal Toxicity with Intravitreal Melphalan Treatment for Retinoblastoma

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Keywords

Retinoblastoma · Posterior segment · Toxicity

Abstract

Background/Aims: The presence of a posterior vitreous detachment (PVD) may play a role in the development of severe retinal toxicity following intravitreal melphalan (IVM) injection for vitreous seeding. We aimed to evaluate the incidence of PVD in retinoblastoma eyes and its association with retinal toxicity after IVM. **Methods:** We reviewed 112 eyes of 81 retinoblastoma patients with B-scan images available for review from 2010 to 2017. A cohort with vitreous seeding treated with IVM was compared to a cohort that did not undergo injection. The primary outcome measure was the presence of PVD at diagnosis and after treatment. Secondary measures included IVM-associated retinal toxicity and other ocular complications. **Results:** The incidence of PVD was 20% at diagnosis, and in eyes with B-scans available both at diagnosis and after treatment 18% of eyes developed a PVD over the course of therapy, more frequently after IVM ($p = 0.05$). Of 34 eyes receiving IVM treatment, the incidences of posterior segment toxicity and globe salvage were similar between eyes with and without PVD ($p = 0.4015$ and

0.52, respectively). **Conclusion:** In this cohort of patients, there did not appear to be an association with the presence of PVD during IVM and the development of retinal toxicity.

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Introduction

Advanced intraocular retinoblastoma is characterized by large retinal tumors which grow in an endophytic fashion (towards the vitreous cavity) or an exophytic fashion (under the retina, causing an exudative retinal detachment) [1]. One of the primary difficulties in the treatment of retinoblastomas has been eradicating vitreous seeds which are small foci of active tumor cells that proliferate in the vitreous cavity. Without a blood supply, they often persist following systemic and/or intra-arterial chemotherapy and are not amenable to treatment with focal modalities. Persistent vitreous seeding is a common cause for treatment failure and the need for secondary enucleation in retinoblastoma [2, 3].

In recent years, intravitreal melphalan (IVM) injection has been introduced as a safe and effective treatment modality for vitreous seeding [4–6], with a success rate of up

to 100% control for vitreous seeding across multiple studies [7–9]. While targeted use of IVM for vitreous seeding has virtually eliminated external beam radiation therapy and its associated risk of second cancers [10, 11], this new modality is not without its own risk of toxicity. Studies have demonstrated a dose-dependent toxic effect on retinal pigment epithelial cells [2, 9, 12] ranging from localized changes which have no effect on vision to diffuse chorioretinal toxicity with irreversible vision loss [3, 13, 14]. IVM has also been associated with anterior segment ocular toxicity, including cataract, anterior chamber inflammation, and iris atrophy [15]. While significant and permanent ocular complications appear to be uncommon with IVM [6, 12, 13, 16], an understanding of the mechanisms and risk factors for any associated ocular toxicity is of paramount importance in this patient group.

It has been hypothesized that the presence of a posterior vitreous detachment (PVD) may play a role in the development of severe, Grade 5 retinal toxicity following IVM [14]. This hypothesis was generated from 2 cases of acute hemorrhagic toxicity wherein a sharp demarcation was noted between the normal and affected retina, suggesting that the melphalan may have been inadvertently injected in the retrohyaloidal space, thus concentrating the drug against the retina. This hypothesis was further supported by the presence of a PVD in both cases, which was not appreciated at diagnosis. Thus, the aim of this study was to:

1. evaluate the incidence of PVDs in retinoblastoma eyes at diagnosis or at any point during the course of therapy and
2. to correlate the presence of a PVD with the risk of developing retinal toxicity secondary to IVM injections for the treatment of vitreous seeding.

Materials and Methods

We conducted a retrospective chart review with data collection spanning the time period between January 1, 2010, to July 30, 2017. The Institutional Review Board at Children's Hospital Los Angeles (CHLA) approved this study and follows the tenets of the Declaration of Helsinki. Patients diagnosed at CHLA with retinoblastoma in at least 1 eye who had posterior segment B-scan ultrasound (using Eye Cubed, Ellex, Adelaide, SA, Australia) images available for review were included. Patients with only written documentation of B-scan findings (e.g., no images available for review) were excluded.

Ultrasound Protocol

New patients diagnosed with retinoblastoma undergo B-scan ultrasound using a 20-Hz probe during the initial examination under anesthesia (EUA) for staging. This is done to measure the tumor,

Table 1. Baseline characteristics of 112 eyes of 81 patients diagnosed with retinoblastoma with B-scan ultrasonography

Median age at diagnosis (range), months	7 (98)
Eyes of female patients	54 (48%)
Right eyes	60 (54%)
Retinoblastoma staging IIRC/TNM	
Group A eyes/cT1a	11 (10%)
Group B eyes/cT1b	27 (24%)
Group C eyes/cT2a	6 (5%)
Group D eyes/cT2b	50 (45%)
Group E eyes/cT3	18 (16%)
IIRC, International Intraocular Retinoblastoma Classification.	

evaluate for intralesional calcification, assess the extent of retinal detachment, and, for very large tumors, ensure no anterior extension (which would require subsequent ultrasound biomicroscopy). Subsequent B-scan ultrasonography is done as clinically indicated, such as in the setting of a persistent retinal detachment. Per the initial protocol described by Munier et al. [4], an ultrasound biomicroscopy is indicated to evaluate the quadrant of injection prior to intravitreal injection of chemotherapy. Further, after the report from Aziz et al. [14] hypothesized that PVD may play a role in severe toxicity, a B-scan was recommended before each intravitreal injection, and this protocol is followed at our center.

B-scan evaluation includes screening imaging, including horizontal axial, vertical axial, and transverse scans in all 4 quadrants and longitudinal scans of the macula and any region of interest. The optic nerve is evaluated for adjacent tumor, any signs of thickening, and in the setting of retinal detachment and PVD.

Images

When available, images included in the study were evaluated from the time of diagnosis, during systemic chemotherapy, before and after IVM therapy was initiated. An ophthalmologist evaluated the images and graded them as PVD present, absent, or indeterminate. Indeterminate scans underwent a second evaluation by another reader. The physicians reading the images were blinded to the clinical and treatment details of the patient.

Treatment

The protocol for systemic chemoreduction at CHLA has been published previously [17]. In brief, Group B eyes are treated with 3 cycles [18], Group C eyes with 4–6 cycles, and Group D and E eyes with 6 cycles of intravenous chemoreduction. Infants <6 months of age at diagnosis receive a modified dosing regimen, which has been described [19]. Unilateral Group D eyes in children >6 months of age may receive primary intra-arterial chemotherapy.

Patients were treated with IVM injections for persistently active or recurrent vitreous seeds following primary chemotherapy. For clinically significant vitreous seeds that persisted or progressed during systemic chemotherapy, we initiated IVM injections during cycles 4–6. For recurrent vitreous seeds after cycle 6 of systemic intravenous chemotherapy (CEV), the typical protocol was 3 weekly IVM injections (often with concomitant laser consolidation of retinal tumors). However, the decision to perform IVM was

Table 2. Incidence of PVD in retinoblastoma at diagnosis with B-Scan ultrasonography and incidence of PVD in retinoblastoma after treatment in 65 eyes of 49 patients with B-scan ultrasonography at diagnosis and during treatment

	With PVD at diagnosis	Without PVD at diagnosis	Indeterminant PVD at diagnosis	Development of PVD with treatment (of 45 eyes without PVD or with indeterminate PVD at diagnosis)
All eyes at diagnosis (112 eyes)	22 (20)	65 (58)	25 (22)	
Group A eyes/cT1a, of 11	0 (0)	11 (100)	0 (0)	
Group B eyes/cT1b, of 27	1 (4)	26 (96)	0 (0)	
Group C eyes/cT2a, of 6	1 (17)	4 (66)	1 (17)	
Group D eyes/cT2b, of 50	14 (28)	22 (44)	14 (28)	
Group E eyes/cT3, of 18	6 (33)	2 (11)	10 (56)	
Eyes with B-scan available during treatment (65 eyes)	20 (31)	36 (55)	9 (14)	8 (18)
Group A eyes/cT1a, of 7	0 (0)	7 (100)	0 (0)	0 (0)
Group B eyes/cT1b, of 20	2 (1)	18 (99)	0 (0)	1 (2)
Group C eyes/cT2a, of 4	1 (25)	2 (50)	1 (25)	2 (4)
Group D eyes/cT2b, of 29	14 (48)	8 (28)	7 (24)	4 (9)
Group E eyes/cT3, of 5	3 (60)	1 (20)	1 (20)	1 (2)

Values are number of eyes (%). PVD, posterior vitreous detachment.

made at each EUA based on the presence of tumor activity. Injections were given until there were no clinical signs of active vitreous seeding; in some patients, this required fewer than 2–3 injections and in other eyes more than 3 injections. In our cohort, we *did not* perform an additional injection after the resolution of vitreous seeding as has been described at other centers [20].

The intravitreal chemotherapy injection procedure for vitreous seeding in retinoblastoma eyes at CHLA closely follows the protocol initially described by Munier et al. [4] and previously published by our center [14, 21, 22].

Ultrasound biomicroscopy was performed prior to the first injection to rule out ciliary body involvement, and B-scan ultrasonography was performed prior to each injection to evaluate for a PVD as per above.

Toxicity

Retinal toxicity was defined by the system proposed by Munier [3], wherein Grade 1 is salt-and-pepper retinopathy limited to 2 clock hours of peripheral retina anterior to the equator. Grade 2 refers to any retinopathy extending greater than 2 clock hours anterior to the equator. Grade 3 retinopathy encompasses salt-and-pepper retinal pigment epithelium changes and extends posterior to the equator but spares the macula. Grade 4 retinopathy involves the macula, while Grade 5 is characterized by pan-retinopathy with optic atrophy.

Chart Review

At initial evaluation, each patient had a full staging EUA. We classified eyes according to the International Intraocular Retinoblastoma Classification (IIRC) described by Linn Murphree [1] and the AJCC 8th edition TNM classification [23]. A retrospective chart review was done to obtain the following information: age at

diagnosis, gender, laterality of retinoblastoma, length of follow-up, systemic chemotherapy agents used with the number of cycles, dates of first and last cycle of chemotherapy, time to recurrence, time to enucleation, number and dates of IVM injections with exact doses, and visual acuity of the treated eyes at last visit. Complications of therapy, including IVM-associated toxicity, were also recorded.

Statistical Analysis

All statistical analyses were performed using Stata/SE 14.2 (StataCorp LLC, College Station, TX, USA).

Results

A total of 112 eyes of 81 patients were diagnosed with retinoblastoma and had B-scan images either at diagnosis or via the course of therapy available for review and were included. Baseline characteristics of the included eyes are summarized in Table 1. Median age at diagnosis was 7 months (range 0–98). Fifty-four eyes of 112 eyes (48%) were from female patients. The included eyes were classified by the IIRC [1] and TNM [23] with the largest proportion being Group D/cT2b eyes (50 of 112 eyes, 45%). The median follow-up time for all eyes from diagnosis was 31.5 months (interquartile range 28.3 months).

Primary enucleation was performed for 18 eyes (16%) following diagnosis. Of the 94 eyes (84%) that underwent

Table 3. Incidence of melphalan toxicity and globe salvage with IVM treatment in 34 eyes of 26 patients with B-scan ultrasonography

	Anterior segment toxicity	Grade 1–3 toxicity	Grade 4–5 toxicity	Globe salvage
With PVD prior to IVM, of 10	0 (0)	6 (60)	1 (10)	8 (80)
Without PVD prior to IVM, of 15	0 (0)	5 (33)	1 (7)	11 (73)
Indeterminant PVD prior to IVM, of 9	4 (44)	3 (33)	2 (23)	8 (89)

PVD status is based on the status prior to IVM. Values are number of eyes (%). PVD, posterior vitreous detachment; IVM, intravitreal melphalan treatment.

salvage therapy, 4 eyes were treated with intra-arterial chemotherapy and the other 90 eyes with 1–6 cycles of CEV and local consolidation. IVM injections were done as salvage for persistent or recurrent vitreous seeding in 34 eyes (34/112, 30%).

At the time of diagnosis, PVD was present in 22 eyes (20%), PVD was not present in 65 eyes (58%), and PVD was indeterminant, mainly due to a large size of the tumor, in 25 eyes (22%) (Table 2). The proportion of PVD was noted more commonly in Group D (cT2b) and Group E (cT3) eyes, with 28% (14 of 50 eyes) and 33% (6 of 18 eyes), respectively.

In the cohort of 65 eyes (of 112, 58%) with B-scan images available for review at both diagnosis and after primary treatment, PVD was present in 20 eyes (20/65, 31%) and PVD was not present or indeterminate in 45 eyes (45/65, 69%) (Table 2). Of these 45 eyes, 8 eyes (8/45, 18%) developed a PVD after treatment; 6 eyes (6/15, 40%) that underwent IVM treatment and 2 eyes (2/30, 7%) that did not receive IVM treatment developed a PVD after treatment ($p = 0.05$). Of these 8 eyes, the mean time from diagnosis to development of PVD was 9.7 months (standard deviation 6.3). These results are summarized in Table 2.

Of 34 eyes that underwent IVM treatment for vitreous seeding, 10 eyes (30%) had a PVD at diagnosis, 15 eyes (44%) did not, and 9 eyes (26%) were indeterminate for PVD at diagnosis. For the eyes that received systemic chemotherapy and received IVM treatment, the percentage of eyes that had PVD at diagnosis was similar to the overall cohort. After IVM treatment, PVD was present in 16 eyes (47%), PVD was not present in 11 eyes (32%), and the presence of PVD was indeterminate in 7 eyes (21%); 6 of 15 eyes (40%) without the presence of PVD prior to IVM developed PVD after IVM with a mean time from diagnosis to development of PVD of 11.7 months (standard deviation 8.3).

For the 34 eyes treated with IVM, 4 eyes (12%) developed anterior segment toxicity: 2 eyes developed a posterior subcapsular cataract and 2 developed focal iris atrophy (Table 3). A total of 18 eyes (53%) developed posterior segment toxicity with 14 eyes (41%) with Grade 1–3 toxicity and 4 eyes (12%) with Grade 4 or 5 toxicity (Fig. 1). A greater percentage of eyes undergoing IVM developed a PVD during therapy compared to the overall cohort (40%, 6/15 vs. 7%, 2/30; $p = 0.05$). However, there was no statistically significant difference between eyes with or without the presence of PVD prior to IVM treatment in the development of either lower-grade chorioretinal toxicity (Grade 1–3) ($p = 0.4136$) or higher-grade chorioretinal toxicity (Grade 4 and 5) ($p = 1.00$) (Fig. 2). The incidence of globe salvage for eyes with, without, and indeterminant for PVD that received IVM treatment was 80% (8 of 10 eyes), 73% (11 of 15 eyes), and 89% (8 of 9 eyes), respectively ($p = 0.52$).

Discussion/Conclusion

This study reports the incidence of PVD at diagnosis or at any point during treatment in patients with retinoblastoma treated at CHLA between 2010 and 2017. To the authors' knowledge, there are no previous reports in the literature regarding the incidence of PVD associated with retinoblastoma; however, 20% of eyes in this cohort were noted to have a PVD at diagnosis, the majority from Group D (cT2b) eyes. This may be due to disruption of the retina-hyaloidal interface from the tumor itself, which is further disrupted with changes in the tumor during the course of therapy. Another hypothesis is that this is due to the presence of vitreous seeds at diagnosis, which may change the vitreous humor dynamics and predispose to the development of PVD. Both hypotheses are supported by the fact that the majority of eyes with PVD at diagnosis

Fig. 1. Patient with retinoblastoma and with posterior vitreous detachment (PVD) prior to intravitreal melphalan (IVM) treatment who developed Grade 5 retinal toxicity after one 20 μ g IVM injection. **a** Fundus photography of retinoblastoma at diagnosis (far left), prior to IVM (left), 1 week after IVM (right), and 6 weeks after IVM (far right). Extensive hemorrhagic retinal toxicity is noted 1 week after IVM (right), which progressed to Grade 5 toxicity with extensive retinal pigment epithelium hyperplasia involving

the fundus and mild optic nerve pallor (far right). Electroretinogram evaluation showed a flat recording. **b** B-scan ultrasonography of the eye at diagnosis was graded as indeterminate; however, a PVD is likely present (left, PVD marked with arrow); prior to IVM the PVD is visualized (middle, PVD marked with arrow). After IVM at the time of acute hemorrhagic toxicity, there is extensive retinal swelling and shallow retinal detachment (asterisk) with a PVD (right, PVD marked with arrow).

Fig. 2. Patient with retinoblastoma and without posterior vitreous detachment (PVD) prior to intravitreal melphalan (IVM) treatment who developed Grade 4 retinal toxicity after IVM. **a** Fundus photography of retinoblastoma at diagnosis (left), prior to IVM (middle), and after IVM (right). Grade 4 retinal toxicity with mac-

ulopathy is noted after IVM (right). **b** B-scan ultrasonography of the eye at diagnosis (left), prior to IVM (middle), and after IVM (right). The absence of PVD is noted prior to and after IVM. The demonstrated maculopathy did not resolve.

demonstrated advanced disease. Over the course of therapy, an additional 18% of eyes developed a PVD. IVM therapy significantly contributes to the development of a PVD; of the 8 eyes that developed a PVD in this study, 6 were from the cohort that were treated with IVM (6/15,

40%) versus 2 that did not require IVM during the treatment course (2/30, 7%) ($p = 0.05$).

Overall, the incidence of a PVD is higher in advanced eyes and more likely to develop in the setting of IVM therapy. Intravitreal injections have been shown to induce a

PVD in adult patients [24]. A more salient question, however, is whether the presence of a PVD is associated with the development of severe, hemorrhagic toxicity as has been previously hypothesized [14]. In the cohort of 34 patients treated with IVM, there was no statistically significant difference between eyes with or without the presence of PVD prior to IVM treatment in the development of either lower-grade chorioretinal toxicity (Grade 1–3) ($p = 0.4136$) or higher-grade chorioretinal toxicity (Grade 4 and 5) ($p = 1.00$). Additionally, as expected, the presence or absence of a PVD was not correlated with globe salvage ($p = 0.52$).

In our cohort of patients, IVM-related toxicities occurred in 65% of eyes following injections, including anterior segment toxicity and any degree of retinal toxicity (Table 3). In this cohort, a total of 18 eyes (53%) developed posterior segment toxicity with 14 eyes (41%) with Grade 1–3 toxicity and 4 eyes (12%) with Grade 4 or 5 toxicity. While a physical mechanism such as an induced PVD for severe Grade 5 toxicity has been described [14], this does not appear to be a likely etiology for all melphalan-related toxicity. The presence of a PVD was not a predictive factor for the development of chorioretinal toxicity secondary to IVM injections in the study. However, it is worth noting that the type of PVD may also contribute to these findings: a complete PVD with a large retrohyaloidal space would not be expected to concentrate the drug against the retina, while a low-lying PVD may contribute to the previously documented findings [14] in the setting of severe toxicity. It is also worth noting that given the inherent difficulties in retrospectively evaluating B-scan images in the setting of tumor and sometimes retinal detachment, these small low-lying PVDs may have been missed on capture (and review) of the ultrasound images.

This study, similar to others that have described the occurrence of severe toxicity, was not able to elucidate one single correlative clinical feature that portends risk of toxicity. More research is warranted to better understand

the risk factors for the development of anterior and posterior toxicity after IVM injection. While PVD was initially suggested to play a role in the development of severe toxicity, analysis of a larger cohort of patients did not lend further support to this hypothesis.

Statement on Ethics

This research complies with the guidelines on human studies and animal welfare regulations. The subjects herein described gave their informed consent, and the study protocol was approved by the Committee on Human Research at the CHLA.

Disclosure Statement

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Author Contributions

Dr. Jesse Berry contributed with data collection, analysis of the data, drafting and review of the manuscript. Dr. Ramon Lee contributed with data collection and drafting of the manuscript. Dr. Luv Patel contributed with data collection and drafting of the manuscript. Ms. Bao Han A. Le contributed with data collection and drafting of the manuscript. Mr. John O'Fee contributed with data collection and drafting of the manuscript. Dr. Rima Jubran contributed with data collection and drafting of the manuscript. Dr. Jonathan Kim contributed with analysis of data and review of the manuscript.

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