HHS Public Access

Author manuscript

Retina. Author manuscript; available in PMC 2022 January 01.

Published in final edited form as:

Retina. 2021 January 01; 41(1): 208–212. doi:10.1097/IAE.0000000000002782.

Toxicity and Efficacy of Intravitreal Melphalan for Retinoblastoma: 25μg vs 30μg

Albert Liao, MD/MS[1,2], **Terry Hsieh, MD/PhD**[1,3], **Jasmine H. Francis, MD**[1,4], **Jessica A. Lavery, MS**[5], **Audrey Mauguen, PhD**[5], **Scott E. Brodie, MD/PhD**[6], **David H. Abramson, MD FACS**[1,4]

[1)]Ophthalmic Oncology Service, Memorial Sloan-Kettering Cancer Center, New York NY 10065

[2)]Emory Eye Center, Emory University School of Medicine, Atlanta, GA 30322

[3)]Stein Eye Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095

[4)]Dept. of Ophthalmology, Weill-Cornell Medical Center, New York, NY 10065

[5)]Dept. of Epidemiology & Biostatistics, Memorial Sloan-Kettering Cancer Center, New York NY 10065

[6]Dept. of Ophthalmology, NYU Langone Health, New York, N.Y. 10017

Abstract

Purpose: To compare retinal toxicity as measured by electroretinogram (ERG), ocular and patient survival in retinoblastoma treated with intravitreal melphalan at two concentrations (25μg vs 30μg).

Methods: Single center, retrospective analysis of retinoblastoma eyes receiving 25μg or 30μg intravitreal melphalan from September 2012 to January 2019. Ocular toxicity was measured by ERG of evaluable injections in 449 injections in 136 eyes. A repeated measures linear mixed model with a random intercept and slope was applied to account for repeated measures for each eye.

Results: Average decline in ERG after each additional injection was −4.9μV (95% confidence interval (CI) −6.3, −3.4); ERG declined by −4.6μV (95% CI −7.0, −2.2) after 25μg injections and −5.2μV (95% CI −6.6, −3.8) after 30μg injections (p=0.66). Injection at a new clock site hour was associated with a −3.91μV lower average (95% CI −7.8, −0.04).

Conclusion: ERG-measured toxicity in retinoblastoma eyes treated with intravitreal injections was not found to be different across 25μg and 30μg injections.

There were no cases of extraocular extension or metastatic deaths in our patient population.

Corresponding author: David H. Abramson, MD, Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, N.Y. 10065, abramsod@mskcc.org.

Disclosure

Alkeran and Evomela, the products used in this study, are not labeled for the use under discussion.

Keywords

Antineoplastic Agents; Drug Effects; Electroretinography; Intravitreal injection; Melphalan; Retina; Retinal Neoplasms; Retinoblastoma; Treatment Outcomes; Vitreous seeds

Introduction

Intravitreal (intravitreous) chemotherapy is now used worldwide to manage vitreous seeding in retinoblastoma eyes. It is effective, not associated with extraocular extension or increased chances of developing metastatic disease but does have ocular toxicities. [1–4] While intravitreal chemotherapy saves eyes that would otherwise been enucleated, this comes at the expense of complications secondary to ocular toxicity. Francis et al previously reported that for every 30μg injection, a concomitant decrease of 5.3μV in ERG measurement occurs; this is likely due to chemotoxicity on the retinal and posterior segment. Treatment may also adversely affect the anterior segment of the eye, including iris recession, iris thinning, and early cataracts. [4,5]

Initial experience with intravitreal melphalan in humans demonstrated that doses less than 10μg were rarely curative and animal experiments suggested that doses above 40μg were severely toxic to retinal function.[3,6] While most centers use doses between 20 and 30μg there are no studies comparing toxicity and efficacy at different doses. Several publications have reported doses ranging from 20–30μg with minimal side effects, to as high as 50μg for refractory disease.[2,6–8] In efforts to minimize ocular toxicity, our practice began standardizing melphalan dosage at 25μg instead of 30μg starting in August 2017. In this report, we specifically evaluated the efficacy, toxicity improvement, and complications of this dosing change using our extensive database of patients and ERG recordings.

Methods

All eyes that received injections of melphalan with or without topotecan for the management of intraocular retinoblastoma from September 2012 to January 2019 were included. The 30μg group was composed of eyes that were treated from September 2012 to November 2017. Several patients received both 25μg and 30μg injections over the course of their treatment. All patients had at least 2 months of follow up from date of first injection with the exception of four patients; 34 patients with ERG analyses were followed more than 2 years. Informed consent was obtained for each patient from their guardian caregiver, or parent. The study was Health Insurance Portability and Accountability Act (HIPAA) compliant and institutional review board (IRB) approval from Memorial Sloan-Kettering Cancer Center was obtained for this retrospective analysis

Injections were performed as follows: after anesthesia induction, intraocular pressure was lowered by digital massage to target pressures of less than 10 mmHg. Intravitreous melphalan (25μg or 30μg in 0.05 to 0.72 mL clear solution) was injected through the conjunctiva, sclera, and pars plana with a 33-gaμge needle 2.5–3.0mm from the limbus; clock of injection was selected based on vitreous seed activity if that was the treatment indication. Prior to needle withdrawal, the injection site was sealed and sterilized with

cryotherapy. Fundus examination was then immediately performed to confirm continued optic nerve perfusion.

The patients were examined under anesthesia; intraocular pressure, external exam, anterior segment assessment, and indirect ophthalmoscopy were all performed. Documentation included fundus drawings, anterior segment and RetCam fundus photography (Clarity, Pleasanton, CA, USA), B-scan ultrasonography (Ellex, Adelaide, Australia), and ultrasonic biomicroscopy (Ellex, Adelaide, Australia). Other exams performed included anterior and posterior segment optical coherence tomography and fundus fluorescein angiography.

Ocular toxicity was quantified through ERG measurements. We used an adaptation of the International Society for Clinical Electrophysiology of Vision standard ERG protocol to obtain electroretinography (ERG) recordings, wherein we utilized the 30-Hz photopic flicker amplitude data as a highly representative surrogate for the complete ISCEV protocol, as previously described.[9] ERGs were recorded using ERG-jet contact lens electrodes and an Espion-3 electrodiagnostic system (Diagnosys, Lowell, MA), with a hand-held ColorBurst ganzfeld stimulator (Diagnosys, Lowell, MA). Measurements were obtained during regularly scheduled examination under anesthesia, immediately prior to each injection, and before any manipulation of the eye. Values at baseline and for each follow-up visit were performed according to International Society for Clinical Electrophysiology Vision (ISCEV) standard protocol. [9]

Patient data collected by chart review included sex, laterality, age, and weight at start of injection course, degree of ocular pigmentation, eye status (enucleated or not), indications for chemotherapy injection (vitreous seeds, subretinal seeds, or retinal tumor), follow-up times from beginning of injection course. Tumor data included Reese-Ellsworth (RE) classification, International Classification of Retinoblastoma (COG Version), and vitreous seed classification at presentation (class 1 = dust, class 2 = sphere +/− dust, class 3 = cloud +/− spheres or dust). Treatment data included number of injections, time interval between injections, concomitant ophthalmic artery chemosurgery (OAC), focal treatment (laser or cryotherapy), use of new injection site clock hour, and concomitant periocular/intravitreous topotecan injection at time of melphalan injection.

Statistical Analysis

Ocular toxicity was evaluated by ERG of evaluable injections. Two data sources were combined for this project, and from the first data source, containing only 30 ug injections, we only had access to injection in which ERG values were recorded. Additional information regarding the first data source has been previously described. [4] For injections beginning December 31st, 2016, we had complete injection information for injections with and without ERG measurements. To be consistent with prior publications all ERG values greater than 100μV were truncated at 100μV due to the inability of the measure to discriminate above that threshold. To analyze the effect of melphalan dose over time, we applied a repeated measures linear model with a random intercept and slope that accounted for repeated measures to each eye. Fixed effects for variables that were significant at a p-value of 0.20 in univariable analyses or of clinical interest were retained for the final model; factors considered were: number of injections, age at injection, weight at baseline, iris color, dose

(25μg, 30μg), formulation (with alcohol, without alcohol), concomitant OAC, and new injection clock site. Interaction terms between injection number and dose as well as injection number and formulation were included to evaluate whether the change in ERG over time varied by dose or formulation. In the primary analyses, all ERG readings were included. A sensitivity analysis was performed excluding ERG readings once an ERG reading is ≤10 to exclude records for which ERG was not high enough to allow ERG change demonstration over the injection course.

In all analyses, eyes from the same patient were considered independent. All statistical analyses were conducted using SAS software (version 9.4; SAS Institute Inc., Cary, NC) and a p-value < 0.05 was considered statistically significant.

Results

A total of 474 injections in 136 eyes were examined (128 patients, eight had bilateral disease). Overall, 110 of all injections were 25μg and 364 injections were 30μg. Overall, 64.1% of eyes received only 30μg injections, 17.2% of eyes only received 25μg injections, and 18.7% of eyes received both 30μg and 25μg injections during their treatment course. Table 1 shows the patient and disease characteristics by injection. Both groups had similar percentages of advanced intraocular disease (Reese-Ellsworth V): 77.3% of injections of patients treated with 25μg melphalan and 76.7% of patients treated with 30μg melphalan. Notable differences among the treated patient population include treatment indication (50.9% of 25μg injections were for non-vitreous seeding versus 24.7% of 30μg injections), concomitant use of OAC (10.0% for 25μg injections and 19.2% for 30μg injections), and concomitant focal treatment with cryotherapy and/or laser (74.5% for 25μg and 35.7% for 30μg).

Of the 474 injections, 449 injections to 135 eyes (128 patients) had an associated ERG reading. Patients received between 1 and 12 injections. The median number of injections was 3. There was a significant association between the number of injections and ERG level; each intravitreous melphalan injection was associated with a −4.9μV (95% CI −6.3, −3.4) decrease in ERG. For the 25μg dose, the average decline in ERG after each additional injection was −4.6μV (95% CI −7.0, −2.2). For the 30μg dose, the average decline in ERG after each additional injection was −5.2μV (95% CI −6.6, −3.8). Reduction in ERG amplitude with each injection was not significantly different between doses (p=0.66). Additional fixed effect variables that were added were age at time of injection, weight at baseline, use of a new injection site, iris color, the presence of alcohol in the formulation and its interaction with injection number. Out of these variables only injection at a new injection clock site hour was significantly associated with retinal toxicity, resulting in an average ERG reading −3.91μV (95% CI −7.8, −0.04) lower compared to an injection at a prior injection site (p=0.05). None of the other included factors were significantly associated with toxicity in the multivariable model (see Table, supplemental digital content 1, which lists the factors used in the multivariable model). In the sensitivity analysis of toxicity excluding injections after ERG is ≤10μV, the multivariable model was additionally adjusted for concomitant topotecan and concomitant OAC. The results regarding dose were similar to the main

analysis (data not shown). There were no disease-related deaths, metastatic disease, or externalization of tumor.

Discussion

Intravitreal chemotherapy has become a widely accepted form of treating patients with retinoblastoma vitreous seeds and has allowed preservation of eyes that would otherwise be enucleated.[6,8,10] However, intravitreal treatments have been shown to have significant, permanent, and irreversible ocular toxicities.[3] Munier et al used a range from 8 μg to 30μg and demonstrated 87% control at 22 months.[2] In a study of 12 patients, Ghassemi and Shields demonstrated that using 8 – 10μg of melphalan hydrochloride achieved 43% long term control with minimal toxic effects (though ERG function was not measured), while 50μg doses saw 100% control long term but resulted in severe adverse side effects such as phthisis bulbi and hypotonia [6]. Other treatment centers have reported use of dosages ranging from 20–45μg.[11,12] Tuncer et al.'s report of 14 injections of 20μg intravitreal melphalan in 7 eyes saw side effects of RPE mottling in two eyes and a required enucleation in one eye.[13]

Starting in August 2017, our practice began treating patients with 25μg injections instead of the 30μg melphalan in the hope that we would have less toxicity without sacrificing efficacy. While the overall decrease of 4.9μV per injection in this study is in line with our previous studies, the decreased dose of 25μg does not appear to reduce toxicity.[3,4] The 5μg decrease appears to be too small to convey a clear toxicity benefit even as treatment sessions accumulate in patients with treatment-refractory disease. Our database did suggest a higher hazard of enucleation after 25μg injections. However, the low number of events prevented us from estimating the dose effect adjusted for important confounding factors such as disease stage, and therefore we were unable to make any conclusion on a true association between dose and risk of enucleation. We encourage further investigation in order to elicit a response to this question.

There have been previous reports of increased rates of melphalan-related toxicities when concurrent systemic treatment was given but fewer reports of the impact of concomitant focal therapy on intravitreal treatment toxicity.[14] Our group previously reported a significant difference in retinal toxicity in patients who received concomitant intra-arterial chemotherapy along with intravitreal melphalan versus those just receiving intravitreal melphalan, a finding that was not seen with the addition of patients with 25μg to our study.[4] A potential explanation to this is that the lower dosing of melphalan negates any synergistic toxicities seen when combined treatments are used at the higher dose. We also saw a significant relationship between injection at a new clock hour site and increased retinal toxicity with the addition of the 25μg cohort. We hypothesize injection at the same clock hour exposes a more limited portion of the retina to the toxic side effect of melphalan, especially at the lower dose.

We also evaluated the change in retinal toxicity following each injection in our multivariable model. We did not find that the level of toxicity increase was different between the 25μg and 30μg dose injections (see Table, supplemental digital content 1, which lists the factors used in the multivariable model). Additional factors examined include both age, weight, and

location of injection, all of which were not associated with increased toxicity. This may alleviate concerns that these variables may lead to increased concentration of drug in the eye, leading to increased toxicity, in our patient population and suggests that intravitreal melphalan can be offered to a wide variety of retinoblastoma patients. We also found that there was no significant difference in retinal toxicity when concomitant focal treatment (cryotherapy and laser) or topotecan injections were given in addition to the melphalan injections (see Table, supplemental digital content 1, which lists the factors used in the multivariable model). This is reassuring in that focal treatments can be used in to control tumor growth without increased risk of toxicity when combined with a more global treatment plan.

The strengths of this paper include the number of patients and injections in our study. Retinal toxicity is objectively quantified using ERG measurements, allowing it to be tracked over individual treatment sessions. In this population of very young children, reliable, reproducible and quantitative measurements of vision are difficult to obtain, thus ERG appears as a valuable criterion in measuring toxicity. The database size allowed us to examine the effects of numerous patient and treatment characteristics on retinal toxicity. As this is a retrospective study, it is not guaranteed that the two populations do not differ in observed or unobserved characteristics. However, the decision to treat with 25 or 30μg was based solely on when the patient was seen in clinic (before or after August 2017), and thus was not influenced by any eye-specific characteristics, leaving less possibility of an unmeasured confounding effect. Additionally, our analysis may oversimplify the complexity of treatment combinations, which are often too complex to be adjusted for, but we believe that we accounted for the main factors that could influence eye toxicity, leading to a fair, although imperfect, comparison between the two doses.

In conclusion, this paper compares the outcomes and treatment effects between patients receiving 30μg melphalan injections and patients receiving 25μg melphalan injections for retinoblastoma. Both doses were associated with measurable degradation of retinal function per injection and there was no significant difference between retinal toxicity between the two treatment groups.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Supported in part by grants from the Fund for Ophthalmic Knowledge, Inc. New York, N.Y. and Cancer Center Support Grant (P30 CA008748). The sponsor or funding organization had no role in the design or conduct of this research.

References

1. Francis JH, Abramson DH, Ji X, et al. Risk of Extraocular Extension in Eyes With Retinoblastoma Receiving Intravitreous Chemotherapy. JAMA Ophthalmol. 2017;135(12):1426–1429. [PubMed: 29098285]

2. Munier FL, Gaillard MC, Balmer A, et al. Intravitreal chemotherapy for vitreous disease in retinoblastoma revisited: from prohibition to conditional indications. Br J Ophthalmol. 2012;96(8):1078–1083. [PubMed: 22694968]

3. Francis JH, Schaiquevich P, Buitrago E, et al. Local and systemic toxicity of intravitreal melphalan for vitreous seeding in retinoblastoma: a preclinical and clinical study. Ophthalmology. 2014;121(9):1810–1817. [PubMed: 24819859]

4. Francis JH, Brodie SE, Marr B, Zabor EC, Mondesire-Crump I, Abramson DH. Efficacy and Toxicity of Intravitreous Chemotherapy for Retinoblastoma: Four-Year Experience. Ophthalmology. 2017;124(4):488–495. [PubMed: 28089679]

5. Francis JH, Marr BP, Brodie SE, Abramson DH. Anterior Ocular Toxicity of Intravitreous Melphalan for Retinoblastoma. JAMA Ophthalmol. 2015;133(12):1459–1463. [PubMed: 26378741]

6. Ghassemi F, Shields CL. Intravitreal melphalan for refractory or recurrent vitreous seeding from retinoblastoma. Arch Ophthalmol. 2012;130(10):1268–1271. [PubMed: 23044940]

7. Ghassemi F, Shields CL, Ghadimi H, Khodabandeh A, Roohipoor R. Combined intravitreal melphalan and topotecan for refractory or recurrent vitreous seeding from retinoblastoma. JAMA Ophthalmol. 2014;132(8):936–941. [PubMed: 24789622]

8. Kaneko A, Suzuki S. Eye-preservation treatment of retinoblastoma with vitreous seeding. Jpn J Clin Oncol. 2003;33(12):601–607. [PubMed: 14769836]

9. Brodie SE, Paulus YM, Patel M, et al. ERG monitoring of retinal function during systemic chemotherapy for retinoblastoma. Br J Ophthalmol. 2012;96(6):877–880. [PubMed: 22426950]

10. Francis JH, Abramson DH, Gaillard MC, Marr BP, Beck-Popovic M, Munier FL. The classification of vitreous seeds in retinoblastoma and response to intravitreal melphalan. Ophthalmology. 2015;122(6):1173–1179. [PubMed: 25795478]

11. Berry JL, Shah S, Bechtold M, Zolfaghari E, Jubran R, Kim JW. Long-term outcomes of Group D retinoblastoma eyes during the intravitreal melphalan era. Pediatr Blood Cancer. 2017;64(12).

12. Kiratli H, Koç İ, Inam O, Varan A, Akyüz C. Retrospective analysis of primarily treated group D retinoblastoma. Graefe's Archive for Clinical and Experimental Ophthalmology. 2018;256(11):2225–2231.

13. Tuncer S, Balci O, Tanyildiz B, Kebudi R, Shields CL. Intravitreal Lower-Dose (20 microg) Melphalan for Persistent or Recurrent Retinoblastoma Vitreous Seeds. Ophthalmic Surg Lasers Imaging Retina. 2015;46(9):942–948. [PubMed: 26469234]

14. Berry JL, Shah S, Kim F, Jubran R, Kim JW. Integrated Treatment during the Intravitreal Melphalan Era: Concurrent Intravitreal Melphalan and Systemic Chemoreduction. Ocul Oncol Pathol. 2018;4(6):335–340. [PubMed: 30574483]

Summary Statement

We did not detect a difference in in toxicity as measured by electroretinogram (ERG) for retinoblastoma eyes treated with 25μg vs. 30μg of intravitreal melphalan. Intravitreal melphalan injections at new sites on the eye was associated with increased ERG-measured toxicity.

Table 1.

Patient and disease characteristics by treatment dosing.

Characteristics	25 ug n (%)	30 ug n (%)
Number of injections	110	364
Number of eyes [a]	49	106
Eye		
OD	54 (49.1)	168 (46.2)
OS	56 (50.9)	196 (53.8)
Age at injection (years)		
Median (range)	3 (1, 16)	3 (0, 18)
Weight (kg) at baseline		
Median (range)	15 (5, 62)	14 (7, 63)
Reese-Ellsworth Stage		
Unknown	0	231
2A	2 (1.8)	2 (1.5)
2B	2 (1.8)	1 (0.8)
3A	3 (2.7)	13 (9.8)
3B	7 (6.4)	5 (3.8)
4A	6 (5.5)	8 (6.0)
4B	5 (4.5)	2 (1.5)
5A	20 (18.2)	7 (5.3)
5B	65 (59.1)	95 (71.4)
International Classification of Retinoblastoma (ICRB)		
Unknown	0	231
1	0 (0.0)	1 (0.8)
2	1 (0.9)	7 (5.3)
3	17 (15.5)	4 (3.0)
4	74 (67.3)	99 (74.4)
5	18 (16.4)	22 (16.5)
Time between injections		
Unknown	0	6
No prior injections	0 (0.0)	1 (0.4)
<=1 week	0 (0.0)	114 (44.4)
1–2 weeks	0 (0.0)	19 (7.4)
2–4 weeks	36 (45.6)	37 (14.4)
4+ weeks	43 (54.4)	86 (33.5)
Iris color		
Blue	16 (14.5)	65 (17.9)
Light brown	5 (4.5)	96 (26.4)
Dark brown	89 (80.9)	203 (55.8)
Seed type		
Non-vitreous	56 (50.9)	90 (24.7)

Characteristics	25 ug n (%)	30 ug n (%)
Vitreous	54 (49.1)	274 (75.3)
Formulation		
No alcohol	110 (100.0)	109 (29.9)
With alcohol	0 (0.0)	255 (70.1)
Concomitant OAC		
No	99 (90.0)	294 (80.8)
Yes	11 (10.0)	70 (19.2)
Concomitant Topotecan		
No	105 (95.5)	312 (85.7)
Yes	5 (4.5)	52 (14.3)
Concomitant focal treatment		
No	28 (25.5)	234 (64.3)
Yes	82 (74.5)	130 (35.7)
New injection clock hour [b]		
Unknown	8	19
No	82 (80.4)	250 (72.5)
Yes	20 (19.6)	95 (27.5)

[a]The same eye could have received 25ug and 30ug injections. Therefore, the sum of the number of eyes from the two columns does not equal the number of eyes in the dataset.

[b]New injection clock site hour was set to “No” for the 1st injection