Intravitreous injection of melphalan hydrochloride is an effective means of treating vitreous seeding of retinoblastoma, and this technique now saves many eyes that once would have been enucleated.1-3 However, each intravitreous injection of melphalan results in a decrement of approximately 5% in retinal function as measured by electroretinography.4 Other groups3,5-7 have confirmed the toxic effects of intravitreous melphalan on the posterior segment of the eye. In this report, we discuss what we believe to be the previously unrecognized topic of anterior segment toxic effects on the eye following intravitreous administration of melphalan.

All injections were performed using a 33-gauge, ½-inch needle with a triplebeveled point and siliconized shaft. The institutional review board of Memorial Sloan Kettering Cancer Center approved this study. Written informed consent had been obtained from all parents, and the institutional review board of Memorial Sloan Kettering Cancer Center provided a waiver for this retrospective study.

The study was conducted at Memorial Sloan Kettering Cancer Center from September 12, 2012, through April 15, 2015; data analysis was performed from April 15 through May 15, 2015.

Report of Cases

Case 1
A toddler with bilateral retinoblastoma had received treatment at an outside institution with systemic chemotherapy, laser therapy, and cryotherapy. The left eye received 4 infusions of ophthalmic artery chemosurgery (OAC) and 3 intravitreous injections of melphalan, 20 μg. He was referred to our institution for a second opinion regarding persistent disease in the left eye. During our initial examination, a needle tract site from a prior intravitreous injection was identified in the lens and appeared as 3 linear, speckled, white punctate lesions (Figure 1). The eyes remain stable and free of tumor at a 14-month follow-up evaluation.

Case 2
A toddler with a diagnosis of unilateral retinoblastoma of the right eye (Reese-Ellsworth group VB, International Classification D) received treatment with 4 cycles of OAC. Persistent dust (class 1) vitreous seeds were noted overlying the main calcified tumor, and the eye received a single intravitreous injection of melphalan, 30 μg. The following week, a Seidel-negative conjunctival bleb was noted in the location of the
intravitreal injection (Figure 1). At the 1-month follow-up examination, the bleb had resolved. The vitreous seeds regressed and, at the 22-month follow-up evaluation, no tumor was noted.

**Case 3**
A young infant with unilateral retinoblastoma of the right eye (Reese-Ellsworth group VB, International Classification C) received 1 cycle of systemic carboplatin, 3 OAC infusions, and treatment with a laser. Persistent vitreous seeds (resembling dust, class I) were identified, and the eye received 5 intravitreal injections of melphalan, 30 μg, the last 2 of which were accompanied by periocular topotecan hydrochloride, 1 mg. All injections at our institution were performed in a manner that has been reported. After the penultimate injection, iris depigmentation and poor dilation were noted spanning the quadrant where the intravitreal injection was administered (Figure 2). Anterior segment optical coherence tomography (OCT) revealed thinning of the iris and loss of crypts compared with the normal iris in the opposite meridian. The child’s disease was inactive and stable at the 13-month follow-up examination.

**Case 4**
A young child with a diagnosis of unilateral retinoblastoma in the left eye (Reese-Ellsworth group VB, International Classification D) received treatment with 2 cycles of OAC. Owing to a cloud (class 3) of vitreous seeds, the eye received 4 intravitreal injections of melphalan, 30 μg. Persistent disease was noted, and the eye was given 3 intravitreal injections of melphalan, 25 μg, and concomitant intravitreous topotecan, 20 μg. After the second intravitreal injection of melphalan and topotecan, retinal necrosis (mimicking a retinotomy), choroidal atrophy, retinal pigment epithelium disturbance, iris recession noted on ultrasonic biomicroscopy, and a hypotensive pressure (5 mg) were noted (Figure 3). The tumor responded, and the eye remained stable at the 4-month follow-up examination.

**Case 5**
A young boy with unilateral retinoblastoma in the left eye (Reese-Ellsworth group VB, International Classification E) received 7 cycles of OAC and 7 intravitreous injections of topotecan, 20 μg, the final 3 of which were combined with intravitreous injections of melphalan, 30 μg. One month after the final intravitreous injections, a geographic area of scleral pigmentation was noted at the injection site. It measured 1 × 0.8 mm with mobile, nonpigmented conjunctiva overlying it, and an anterior segment OCT revealed focal indentation of the sclera (Figure 3). The tumor was inactive, and the eye was stable at the 5-month follow-up examination.

**Discussion**
Several studies, in both humans and animals, demonstrate posterior segment toxic effects from intravitreal administra-
tration of melphalan. For instance, disturbance of the retinal pigment epithelium (salt and pepper retinopathy) is reported to occur in approximately 43% to 50% of patients and has been significantly associated with more pronounced degradation of electroretinographic responses.\textsuperscript{1,4}

Anterior segment abnormalities have been described extensively following intravitreous injections of antivascular endothelial growth factor agents. These findings include scleral thinning after numerous injections, episcleral cystoid cavities,\textsuperscript{9} intraocular inflammation,\textsuperscript{10} corneal edema, Descemet folds,\textsuperscript{11} cataract,\textsuperscript{12} and ocular surface foreign bodies.\textsuperscript{13} In our cohort, we observed anterior abnormalities in 5 patients receiving intravitreous injections of melphalan for retinoblastoma, including a traumatic cataract following injection at an outside hospital, iris depigmentation and thinning, iris recession (in association with retinal necrosis and hypotony), a filtering conjunctival bleb 1 month following the injection, and focal scleromalacia with localized pigmentation. All these abnormalities were found at the injection site or within the meridian of the injection.

The lens opacity induced at the outside hospital can be explained by the surgical technique and has the potential of occurring regardless of the drug being injected. However, the other findings and the extent of the damage can be correlated with the toxic effects of melphalan. The iris depigmentation and thinning can be likened to the salt and pepper retinopathy that is seen in the fundus and is thought to occur from the proximity of the drug to the disturbed surface.\textsuperscript{1,4} In this case, one may speculate whether drug escaped to the anterior chamber, making contact with and damaging the iris stroma. Similarly, the iris recession and hypotony appeared to be an extension of the posterior segment findings of retinal necrosis, choroidal atrophy, and retinal pigment epithelium disturbance and are likely related to elevated drug concentration in the location of the injection. Temporary blebs are often observed immediately following intravitreous injections and presumably result from the reflux of intraocular contents into the subconjunctival space. However, in this instance, the bleb was most apparent 1 week following the injection, perhaps suggesting the refluxed melphalan allowed for continued patency of a potential trans-scleral fistula, resulting in a filtering bleb. Finally, although scleral thinning following administration of bevacizumab has been visualized with OCT,\textsuperscript{9} it seldom involves a rarity of scleral tissue with visualization of the underlying uvea as was seen in our case 5. It is possible that melphalan contributed to atrophy and necrosis of the ocular surface in a manner similar to that found with the iris, choroid, retinal pigment epithelium, and retina.\textsuperscript{1,4,14,15} However, the scleral pigmentation may simply represent migrated deposition of released pigments from nearby retina, ciliary body, or iris.
Conclusions

Intravitreous injection of melphalan has allowed ophthalmic oncologists to salvage eyes that, until recent years, would have been enucleated; however, this benefit does not come without toxic effects on both the anterior and posterior segment. These anterior segment findings are of importance when guiding parents through the intravitreous technique, particularly since many of these features have the potential of being easily observed by the parents without the need for sophisticated equipment.

ARTICLE INFORMATION

Submitted for Publication: May 29, 2015; final revision received July 2, 2015; accepted July 6, 2015.

Published Online: September 17, 2015. doi:10.1001/jamaophthalmol.2015.3119.

Author Contributions: Dr Francis 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.
Study concept and design: Francis, Abramson.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Francis.
Critical revision of the manuscript for important intellectual content: Marr, Brodie, Abramson.
Administrative, technical, or material support: Abramson.
Study supervision: Abramson.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Funding/Support: This work was supported by the Fund for Ophthalmic Knowledge.
Role of the Funder/Sponsor: The Fund for Ophthalmic Knowledge participated in the design and conduct of the study but had no role in the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES


