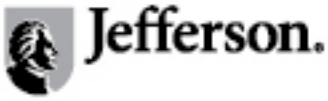

7-1-2017

Intravitreal Melphalan for Treatment of Primary Vitreoretinal Lymphoma: A New Indication for an Old Drug.

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Europe, this practice is less consistently used in the United States. However, these studies do not constitute level I evidence, and thus, there is no worldwide consensus regarding endophthalmitis prophylaxis with cataract surgery.[6]

Limitations. This study is limited by its retrospective nature and the possibility of selection bias. The mechanism of this increasing nonsusceptibility to fluoroquinolones is not fully understood, but it may be associated with widespread use of fluoroquinolones, use of antibiotics outside of the health care sector, and emergence of intrinsic genetic factors promoting resistance. Although this study involves only in vitro testing, the clinical implications of this laboratory data requires further investigations.

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Accepted for Publication: April 9, 2017.

Published Online: June 15, 2017. doi:10.1001/jamaophthalmol.2017.1826

Author Contributions: Drs Stringham and Flynn had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Stringham, Flynn.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Stringham.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: Miller, Flynn.
Supervision: Miller, Flynn.

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 research work was supported in part by National Institutes of Health Center Core grant P30EY014801 and a Research to Prevent Blindness Unrestricted Grant.

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

1. Schimel AM, Miller D, Flynn HW. Evolving fluoroquinolone resistance among coagulase-negative Staphylococcus isolates causing endophthalmitis. *Arch Ophthalmol*. 2012;130(12):1617-1618.

2. Dave SB, Toma HS, Kim SJ. Ophthalmic antibiotic use and multidrug-resistant staphylococcus epidermidis: a controlled, longitudinal study. *Ophthalmology*. 2011;118(10):2035-2040.

3. Kim SJ, Toma HS. Antimicrobial resistance and ophthalmic antibiotics: 1-year results of a longitudinal controlled study of patients undergoing intravitreal injections. *Arch Ophthalmol*. 2011;129(9):1180-1188.

4. Chiquet C, Maurin M, Altayrac J, et al. Correlation between clinical data and antibiotic resistance in coagulase-negative Staphylococcus species isolated from 68 patients with acute post-cataract endophthalmitis. *Clin Microbiol Infect*. 2015;21(6):592.e1-592.e8.

5. Haripriya A, Chang DF, Ravindran RD. Endophthalmitis reduction with intracameral moxifloxacin prophylaxis: analysis of 600 000 surgeries. *Ophthalmology*. 2017;S0161-6420(16)30790-4.

6. Grzybowski A, Schwartz SG, Matsuura K, et al. Endophthalmitis prophylaxis in cataract surgery: overview of current practice patterns around the world. *Curr Pharm Des*. 2017;23(4):565-573.

OBSERVATION

Intravitreal Melphalan for Treatment of Primary Vitreoretinal Lymphoma: A New Indication for an Old Drug

Primary vitreoretinal lymphoma (PVRL) is a malignant large B-cell lymphoma affecting the eye and brain, with 5-year cumulative survival rate of 35% in those with brain involvement (68% in those without).[1] Ocular involvement manifests with aggregated tumor cells in the vitreous, retina, optic disc, and subretinal pigment epithelial space. Management involves treatment of both eyes and brain, and treatment options for the eye(s) include systemic chemotherapy, external radiotherapy, or intravitreal injection of chemotherapy.

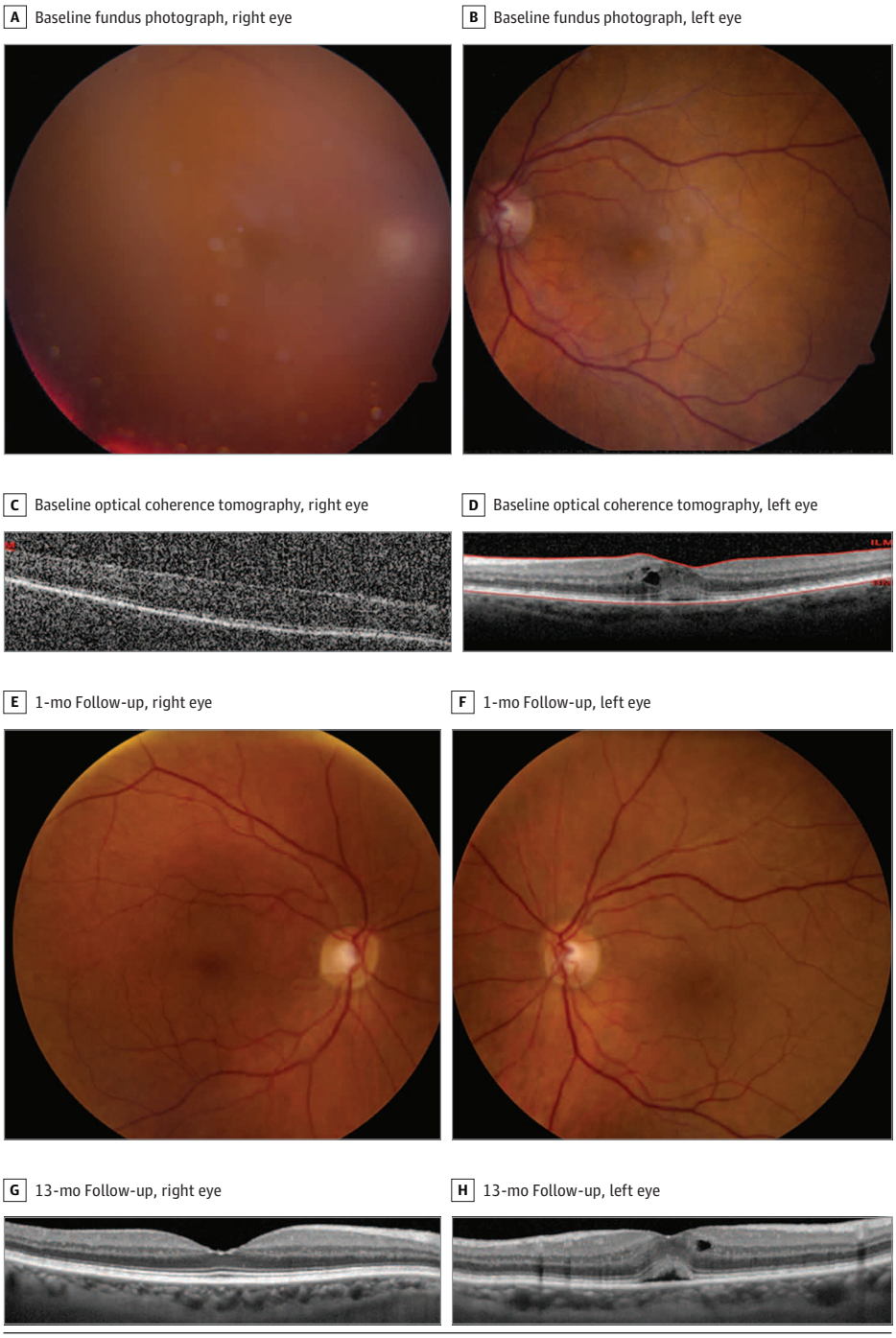
The most commonly used intravitreal medication for PVRL is methotrexate.[2,3] Others have investigated intravitreal rituximab.[4] Herein, we report our experience with melphalan, a medication commonly used for treatment of vitreous seeding from retinoblastoma,[5,6] in 3 eyes of 2 patients with PVRL. Both methotrexate and melphalan have been used for retinoblastoma, and methotrexate requires approximately 25 injections/y, whereas melphalan needs fewer at 4 to 6 injections/y, the latter achieving retinoblastoma seed control in up to 100% of cases.[3,6]

Melphalan is a well-established alkylating agent, developed in 1953 and used to treat several hematologic malignancies, including lymphoma, leukemia, and multiple myeloma, as well as solid tumors including breast, ovarian, and neural cancers.[5] When used in the vitreous for retinoblastoma, filtered preparation of 20 µg/0.1 mL is sufficient for tumor control.[6] Owing to its effect on lymphoma and our experience with this medication, we challenged PVRL with melphalan.

Methods | This retrospective investigation was approved by the institutional review board of Wills Eye Hospital. Three eyes of 2 patients with biopsy-confirmed PVRL were offered standard treatment or intravitreal melphalan (low dose [10 µg/0.1 mL]). Following written consent, the medication was injected into the vitreous using sterile technique. Clinical features and outcomes were recorded.

Results | *Case 1*. A 92-year-old woman with vitrectomy-proven bilateral PVRL (large B-cell lymphoma cytology) demonstrated severe vitreous tumor infiltration in the right eye and mild infiltration in the left eye, with subretinal pigment epithelial tumor in the left eye (**Figure 1**). Visual acuity was 20/30 OD and 20/40 OS. She was treated with low-dose intravitreal melphalan (10 µg/0.1 mL) to both eyes. Following initial injection, complete clearance of vitreous tumor in both eyes was noted within 3 weeks. During the 19-month follow-up, the right eye required 6 bimonthly injections for minor seed recurrence, and the left eye remained stable without recurrence. There were no toxicities in either eye, but the left eye showed stable focal subfoveal fluid, with mild macular edema at presentation and throughout her course. Final visual acuity was 20/50 OU.

Figure 1. Case 1: A 92-Year-Old Woman

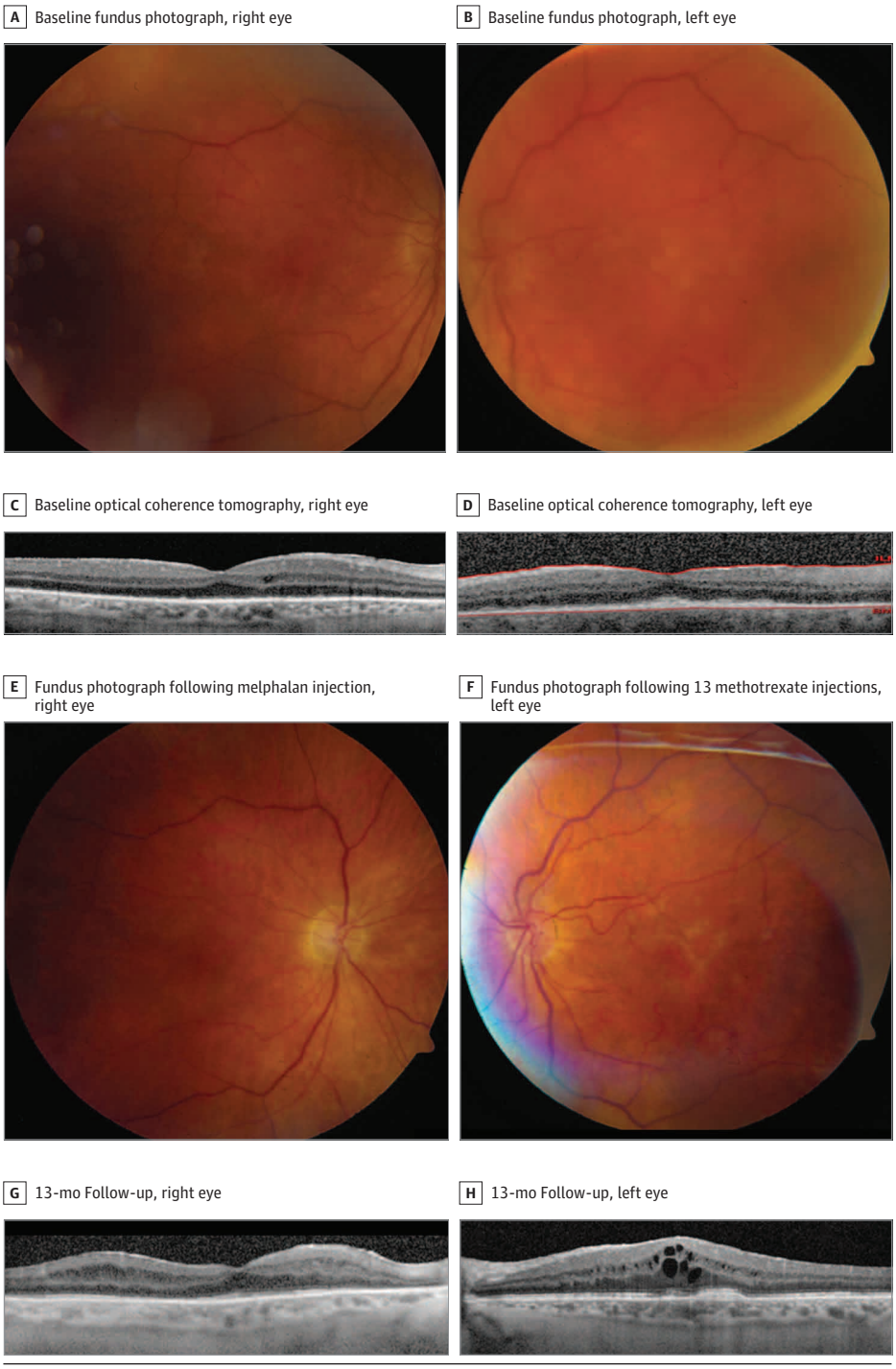


A 92-year-old woman with visual acuity of 20/30 OD and 20/40 OS and biopsy-proven posterior vitreoretinal lymphoma showed dense vitreous infiltrate in the right eye (A) and mild vitreous infiltrate in the left eye (B) with peripheral multifocal retinal pigment epithelial infiltrates. Optical coherence tomography showed hazy view of the fovea in the right eye from vitreous opacification and intraretinal edema with shallow subretinal fluid in the left eye (C and D). Following 1 injection of intravitreal melphalan to each eye, complete clearance of vitreous cells was documented in both eyes (E and F) at 1 month. Optical coherence tomography showed a normal right fovea (G) and unchanged edema and subretinal fluid in the left eye (H). Final visual acuity was 20/50 OU at 16 months' follow-up.

Case 2. A 65-year-old man with chronic uveitis in both eyes and vitrectomy-proven PVRL (large B-cell lymphoma cytology) demonstrated moderate vitreous tumor in both eyes (**Figure 2**). At treatment, visual acuity was 20/150 OD and 20/400 OS. The right eye was treated with intravitreal melphalan and the left eye with intravitreal methotrexate. The right eye demonstrated rapid improvement of visual acuity within 2 days (per patient observation) and measured 20/50 at 1 month, requiring no further melphalan injections over 16 months follow-up, whereas the left eye showed slower response and a total of 19 injections of methotrexate over 11 months follow-up. Both eyes showed intermittent cystoid macular edema from uveitis, and final visual acuity was 20/50 OD and 20/70 OS.

A summary of the 3 eyes with PVRL revealed rapid response to low-dose intravitreal melphalan, with complete vitreous tumor clearance in 2 cases following a single injection and tumor control following multiple injections in one case. There was no retinal toxicity.

Figure 2. Case 2: A 65-Year-Old Man



A 65-year-old man with visual acuity of 20/150 OD and 20/400 OS with chronic posterior uveitis and biopsy-proven posterior vitreoretinal lymphoma showed moderate vitreous infiltrate in both eyes at the time of treatment (A and B). Optical coherence tomography showed trace macular edema in the right eye (C) and shallow subretinal debris in the left eye (D). Following a single melphalan injection in the right eye (E), complete clearance of vitreous cells was documented and persisted until last examination. Following 13 injections of methotrexate in the left eye (F), vitreous clearance was noted. At last examination, optical coherence tomography documented trace foveal edema in the right eye (G) and moderate macular edema in the left eye (H). At 13 months, final visual acuity was 20/50 OD and 20/70 OS.

Discussion | These 3 eyes with PVRL demonstrate that intravitreal melphalan, currently used for vitreous seeds from retinoblastoma,[6] can result in vitreous lymphoma control with few injections. Given the limited number of cases and relatively short follow-up, further investigation seems warranted to determine efficacy, safety, and appropriate treatment regimen.

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Published Online: June 15, 2017. doi:10.1001/jamaophthalmol.2017.1810

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: Support provided by Eye Tumor Research Foundation, Philadelphia, Pennsylvania (Dr Carol L. Shields).

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We thank Emil A. Say, MD, Oncology Service, Willis Eye Hospital, Philadelphia, Pennsylvania, for his contribution to patient care. No compensation was received from a funding sponsor for such contributions.

1. Riemens A, Bromberg J, Touitou V, et al. Treatment strategies in primary vitreoretinal lymphoma: a 17-center European collaborative study. *JAMA Ophthalmol*. 2015;133(2):191-197.

2. Levasseur SD, Wittenberg LA, White VA. Vitreoretinal lymphoma: a 20-year review of incidence, clinical and cytologic features, treatment, and outcomes. *JAMA Ophthalmol*. 2013;131(1):50-55.

3. Frenkel S, Hendler K, Siegal T, Shalom E, Pe'er J. Intravitreal methotrexate for treating vitreoretinal lymphoma: 10 years of experience. *Br J Ophthalmol*. 2008;92(3):383-388.

4. Larkin KL, Saboo US, Comer GM, et al. Use of intravitreal rituximab for treatment of vitreoretinal lymphoma. *Br J Ophthalmol*. 2014;98(1):99-103.

5. Bayraktar UD, Bashir Q, Qazilbash M, Champlin RE, Ciurea SO. Fifty years of melphalan use in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2013;19(3):344-356.

6. Shields CL, Douglass AM, Beggache M, Say EA, Shields JA. Intravitreous chemotherapy for active vitreous seeding from retinoblastoma: outcomes after 192 consecutive injections: the 2015 Howard Naquin Lecture. *Retina*. 2016;36(6):1184-1190.

COMMENT & RESPONSE

Patient Coauthored History Could Improve Health Record Accuracy

To the Editor The article by Valikodath et al[1] showcases a problem with modern health records: documentation does not always match the patient's concerns. The authors conclude that electronic medical record data may not provide a comprehensive resource for clinical practice or "big data" research.

I agree that a solution may come from patient-generated information. In a previous report,[2] patients were invited to complete a replica of a history as defined by the Centers for Medicare and Medicaid Services. Patients completed a 3-page prehistory form with approximately 30 questions in a structured format that included chief complaint(s), a history of present illness, the status of chronic condition(s), a review of systems, and a past family social history.[3]

A total of 263 patients who were aged 14 to 94 years completed the form in preparation for a family physician visit. On arriving to the office, the prehistory form was scanned into the electronic health record as a document and the content was transcribed by a staff member into the history component of the encounter note. The prehistory was recognized as a written request to amend the health record per the Health Insurance Portability and Accountability Act Privacy Rule (45 C.F.R. § 164.526).

I was the physician who conducted the medical encounters for patients with a prehistory and I can attest to the improvement in medical record accuracy. I was able to enter the examination room, greet the patient, and then read the patient's narrative, all of which was documented in the record. I finished the history with specific questions and then performed a pertinent examination. Any medical decision making occurring readily transformed to shared decision making because the patients were engaged and I was relieved of clerical burdens.

After seeing the physician, each patient was given a paper copy of the encounter note at the checkout window. Patients were instructed to go home, read their record, and score it with an anonymous survey. Patients who completed a prehistory form in preparation for a medical encounter reported feeling better heard and understood.

Medical record inaccuracy could adversely affect patient safety and data analytics. These comments suggest that a prehistory form potentially may be a means of improving health record accuracy.

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Published Online: June 8, 2017. doi:10.1001/jamaophthalmol.2017.1637

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Editorial Note: This letter was shown to the corresponding author of the original article, who declined to reply on behalf of the authors.

1. Valikodath NG, Newman-Casey PA, Lee PP, Musch DC, Niziol LM, Woodward MA. Agreement of ocular symptom reporting between patient-reported outcomes and medical records. *JAMA Ophthalmol*. 2017;135(3):225-231, 231.

2. Warner MJ, Simunich TJ, Warner MK, Dado J. Use of patient-authored prehistory to improve patient experiences and accommodate federal law. *J Am Osteopath Assoc*. 2017;117(2):78-84.

3. Patient Advocacy Initiatives. PreHistory forms available for free at non-profit: http://www.PatientAdvocacyInitiatives.org. Accessed February 16, 2017.

Incorporating Clinical, Histological, and Genetic Parameters for Choroidal Melanoma Prognostication

Walter et al[1] recently reported that tumor diameter measurement enhances the prediction of metastatic disease from class 2 uveal melanoma (UM), as classified with gene expression profiling. They advocate combining these 2 predictors when estimating prognoses.

We agree with this recommendation. Since 2007, we have published several articles emphasizing the importance of combining clinical, histologic, and genetic survival predictors when estimating a prognosis for UM posttreatment.[2] We developed an online prognostic tool predicting survival using multivariable analyses, also accounting for age and sex.[2] Walter et al[1] have not cited these articles, so their Discussion does not interpret their results by taking into consideration all other relevant evidence in the literature.