Serous retinopathy associated with MEK inhibition (binimetinib) for metastatic cutaneous and uveal melanoma

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Purpose: To analyse the clinical characteristics of a serous retinopathy associated with MEK inhibition with binimetinib for metastatic cutaneous melanoma (CM) and uveal melanoma (UM), and to study possible pathogenetic mechanisms that may lead to this retinopathy.

Methods: An extensive ophthalmic examination was performed in all patients, including Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) measurement, slit lamp examination, indirect ophthalmoscopy, fundus photography, and optical coherence tomography. In selected cases, additional examinations were performed, including central visual field analysis, fundus autofluorescence, fluorescein angiography, electro-oculography (EOG), and electroretinography (ERG). Blood samples were obtained from 3 CM and 3 UM patients to analyze the presence of autoantibodies against retinal and retinal pigment epithelium (RPE) proteins.

Results: Six CM (20%) and 2 UM patients (40%) reported visual complaints during the study. The mean time until the onset of visual complaints, which were mild and transient in all patients, was 6 days (range, <1 hour-3 weeks). On OCT, serous subretinal fluid (SRF) was detected in 77% of CM patients, and in 60% of UM patients. The SRF affected the fovea in 85% of CM patients and 81% of UM patients. In 19 eyes of 11 patients an EOG was performed after the start of the binimetinib medication: 16 of these eyes (84%) developed SRF on OCT. Fifteen (94%) of these eyes showed an abnormal Arden ratio (<1.65), and 1 eye (6%) showed a subnormal Arden ratio (1.65-1.8). A broad pattern of anti-retinal antibodies was found in 3 CM and 2 UM patients. Anti-RPE-antibodies were detected in all 6 patients. Anti-bestrophin antibodies were detected in 3 patients.

Conclusions: A time-dependent and reversible serous retinopathy can develop in CM patients and UM patients treated with binimetinib or a combination of binimetinib and sotrastaurin. A minority of patients develop visual complaints, which are generally mild and transient. A possible cause of binimetinib-associated serous retinopathy may be toxicity of study medication, but autoantibodies can also be involved.

Commercial Relationships: Camiel J. Boon, None; Elon H. van Dijk, None; Carla M. van Herpen, None; Marina Marinkovic, None; Drake Amundson, None; Gregorius P. Luyten, None; Martine J. Jager, None; Ellen H. Kapiteijn, None; Jan E. Keunen, None; Grazyna Adamus, None.
The choroidal thickness decreased significantly to 256.53 ± 62.92 (P=0.024) at 6 months after treatment. No significant association between the changes of choroidal thickness and the changes of ultrasonographic tumor characteristics such as LBD and apical height was found.

**Conclusions:** The eyes with choroidal melanoma showed increased subfoveal choroidal thickness. The choroidal thickness decreased after successful treatment of local tumor therapy. Further investigation is necessary to study the implication of subfoveal choroidal thickness assessment in the management of choroidal melanoma.

**Commercial Relationships:** SungChul Lee, None; Ji Hwan Lee, None; Hyesun Kim, None; Jong Kyoung Na, None; SungChul Lee

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**Presentation Time:** 11:00 AM–12:45 PM

**Serum analysis of a patient with paraneoplastic exudative polymorphous vitelliform maculopathy and multiple myeloma**

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**Purpose:** The Retina Eye Center, Augusta, GA

**Program Number:** 3439 **Poster Board Number:** C0250

**Presentation Time:** 11:00 AM–12:45 PM

**Local control after stereotactic photon treatment of uveal melanoma analysis.**

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**Purpose:** Radiotherapy offers patients with malignant melanoma of the choroid a vision-sparing alternative to enucleation. The most commonly used forms of radiotherapy are ophthalmic plaque brachytherapy and external beam irradiation such as proton beam and stereotactic radiotherapy that typically involves a column of radiation directing through the anterior structures in order to reach the intraocular tumor causing complications like eyelash loss, eyelid excoriation, corneal neovascularization and ulceration, dry eye, neovascular glaucoma.

Varian TrueBeam Stereotactic Radiotherapy is a new option using a non filtered photons rapidarc VMAT (Volumetric Modulated Arc Therapy) dynamically delivered that shortens the irradiation time. We report our experience with this technique in the treatment of choroidal melanoma.

**Methods:** Between February 2012 and November 2012, 15 patients affected by choroidal melanoma were treated with stereotactic radiotherapy (SRT) with VMAT with flattening filter-free (FFF) on a Varian™ TrueBeamStx. Acute toxicity was recorded. Local control evaluation was scored by means of Ocular A and B scan ultrasound examination, anterior segment and fundus examination, fluorescein and indocyanine angiography, intraocular pressure measurement and CT /PET scan.

**Results:** Patients were 5 males and 10 females, with a median age of 71.3 years (range, 65–78 years). The mean sizes of the lesions were base: 12.67 mm (range 10-16.1 mm) and high: 8.25 mm (range 4-12.5mm). The prescribed radiation dose was 27 Gy in 1 fraction to CTV. The median follow-up was 10.5 months (range: 5–22 months). All patients completed the treatment. Until today there were no cases of local progression and no enucleations. Up to now complications were 1 cataract, 1 hemovitreous and 1 retinal ischemia.

**Conclusions:** Data of dosimetrical findings and acute toxicity are excellent for patients with choroidal melanoma treated with SRT with VMAT using FFF beams. Preliminary clinical results showed a high rate of local control in irradiated patients with a low incidence of toxicity. The VMAT is delivered in a dynamic way with the radiation source in motion during dispensing thus allowing greater speed of delivery of dose, focusing radiation on tumor tissues and reducing the risk of collateral damage to healthy organs. Further data and longer follow up are needed to assess late toxicity and definitive clinical outcomes.

**Commercial Relationships:** Federica Genovesi-Ebert, None; Maria Grazia Fabrini, None; Federica Cresti, None; Franco Perrone, None; Claudia Belting, None; Emanuele Di Bartolo, None

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Photodynamic Therapy for Symptomatic Choroidal Nevi in 23 Cases

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Purpose: To report the outcome of treatment of symptomatic choroidal nevus with photodynamic therapy (PDT).

Methods: Retrospective interventional case series of 23 eyes with symptomatic choroidal nevi, from subfoveal fluid or cystoid macular edema, treated with standard PDT.

Results: Mean patient age was 52 years (range, 13-73 years). Mean tumor thickness and diameter were 2 mm (range, 0.8-3.4 mm) and 5 mm (range, 4.5-9 mm) respectively, and the mean tumor distance to foveola was 1 mm (range, 0.6-2.0 mm). 18 nevi (78%) were melanotic, 4 (17%) amelanotic, and 1 mixed. Mean number of PDT sessions was 1.4 (range, 1-2). Among the 19 patients (82%) who had subretinal fluid in fovea (SRF) before PDT, 12 (63%) showed resolution of SRF, which was complete in 6 patients and partial in the other 6. At mean follow-up of 46 months, 3 of 12 patients with prior SRF resolution developed recurrent SRF. Among the 5 patients who had cystoid macular edema (CME) before PDT treatment, 3 had CME resolution after PDT. Of 18 patients with visual acuity of 20/40 or less before PDT, 6 (33%) had improved visual acuity. 8 (44%) had stable visual acuity and 4 (22%) had worse visual acuity following PDT. Retinal pigment epithelial atrophy at the site of PDT application developed in 1 patient, but no other complications related to PDT were noted. Two patients (9%) showed growth of nevi into choroidal melanoma and were treated with radioactive plaque and transpupillary thermotherapy.

Conclusions: PDT is a safe and effective treatment modality, leading to resolution of SRF and CME in about 60% of patients with symptomatic choroidal nevi.

Commercial Relationships: Wasis A. Samara, None; Choe T. Kho, None; Renelle Pointdujour Lim, None; George Magrath, None; Arman Mashayekhi, None; Jerry A. Shields, None; Carol L. Shields, None.
Results: Principal component analysis shows clustering of samples by 3 groups: retinoblastoma, retinocytoma, and normal retina. Analysis of only the retinoblastoma samples shows clustering of tumors with mild, moderate, and severe anaplasia. Unsupervised hierarchical clustering reflected groupings similar to those obtained by PCA. Highly enriched gene ontology categories were those associated with photoreceptor differentiation and phototransduction in normal retina, transcription regulation and nuclear organization in retinocytoma, and cell cycle and mitosis in retinoblastoma.

Conclusions: Gene expression profiling demonstrates differential expression between normal retina, retinocytoma, and retinoblastoma. Progression from retinocytoma to retinoblastoma may be secondary to compromised gene regulation and expression resulting in modifications in nuclear organization manifested phenotypically as cellular anaplasia.
Intravitreal anti-VEGF therapy has limited benefit in treating radiation retinopathy following iodine-125 radiotherapy for the treatment of choroidal melanoma

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Purpose: Although the use of anti-vascular endothelial growth factor (VEGF) inhibitors has emerged as a common treatment for radiation macular edema following plaque radiotherapy for choroidal melanoma, studies evaluating long-term protective benefits of bevacizumab in vision and macular edema are limited. We performed a retrospective consecutive review to elucidate the outcomes and efficacy duration of the intravitreal anti-VEGF agent bevacizumab in patients who developed radiation retinopathy following iodine-125 brachytherapy for local treatment of choroidal melanoma.

Methods: All patients at the Ophthalmic Oncology Center at the Stein Eye Institute who received at least one intravitreal anti-VEGF in the form of bevacizumab, for the treatment of radiation retinopathy evidenced by macular edema following iodine-125 brachytherapy for the treatment of choroidal melanoma from 2001-2013 were included. Patient and baseline tumor characteristics were recorded; treatment response was evaluated by reviewing best recorded Snellen visual acuity (BRVA) and foveal thickness measured by spectral domain optical coherence tomography (SD-OCT).

Results: Forty-two patients received bevacizumab injection initiated at a mean of 38 months (range 3-310) following iodine-125 brachytherapy with a mean of 5 injections (range 1-18) over 8 months with mean follow-up time of 19 months (range 1-66) following first injection. BRVA at final follow-up was 20/215, a statistically significant decline from a pre-injection baseline of 20/76 (p=0.0056). BRVA at one month was 20/74, not statistically different from baseline (p=0.9348). Baseline mean SD-OCT foveal thickness was 440 mm. No differences in foveal thickness were found at one month or final follow-up, with mean foveal thicknesses of 382 mm (p=0.1180) and 387 mm (p=0.1535), respectively.

Conclusions: Bevacizumab may not improve visual acuity nor SD-OCT foveal thickness in patients who develop radiation retinopathy with macular edema. Any benefits of anti-VEGF therapy with bevacizumab appear to not be sustained.

Commercial Relationships: Elisha C. Garg, None; Peter Custis, None; Robert E. Engstrom, None; Scott Grant, None; Glen Jarus, None; Richard Pesavento, None; Dante J. Pieramici, None; Colin A. McCannel, None; Tara A. McCannel, None

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Treatment of subretinal fluid associated with choroidal nevus

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Purpose: To report the outcomes of 15 patients with subretinal fluid associated with choroidal nevus.

Methods: The medical records of 15 patients who diagnosed with choroidal nevus between December 2005 and July 2014 were retrospectively reviewed. All patients were examined with fluorescein angiography, fundus photo, B-scan ultrasonography and optical coherence tomography. Patients were treated with intravitreal bevacizumab (IVB) and/or transscleral thermotherapy (TTT) or observed without treatment. Data were analyzed to evaluate outcomes of treatment response and visual acuity.

Results: Fifteen patients were included in this study. Of this, eight patients were treated with only IVB, two patients with only TTT, four patients with TTT following IVB and one patient observed without treatment. Visual acuity improved in four eyes by more than 2 Snellen lines, remained stable in six eyes, and worsened in five eyes by more than 2 Snellen lines. Among twelve patients who treated with IVB (1–6 injections), only one patient showed complete subretinal fluid reduction on OCT but no vision improvement was observed. Two patients who treated with TTT showed complete fluid absorption and vision improvement. Among 4 patients who treated with TTT and IVB, one patient showed complete fluid absorption after TTT, which did not respond to IVB. Spontaneous subretinal fluid absorption was observed in two patients (one patient; without treatment, one patient; 3 years after last IVB). Six choroidal nevus demonstrated tumor growth after IVB and treated with brachytherapy or enucleation.

Conclusions: Intravitreal bevacizumab injection showed no sufficient effect in reducing vision threatening subretinal fluid associated with choroidal nevus, but transscleral thermotherapy seems effective in reducing fluid and improving vision. Spontaneous subretinal fluid absorption may occur without treatment. The growth of choroidal nevus was noted and treated as choroidal melanoma, so careful monitoring for tumor growth is necessary.

Commercial Relationships: Hee Jung Kwon, None; Jimin Ahn, None; Christopher Seungkyu Lee, None; Min Kim, None; SungChul Lee, None

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Identification of molecular signatures specific to clinical and histopathological grades of retinoblastoma in primary enucleated eyes

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Purpose: Our study compares the clinical classification of retinoblastoma (Rb) with histopathological risk in enucleated eyes and attempts to identify a gene expression pattern that shows unique correlation to each group.

Methods: We retrospectively studied 58 enucleated eyes with intraocular Rb, and excluded 19 eyes that had received pre-enucleation chemotherapy or focal therapy. Classification at presentation was determined using the IIRC system for the 39 eyes included. We collected 9 fresh frozen tumor samples and subjected them to microarray analysis to define gene expression patterns. Written, informed consent and approval of the Institutional Ethics Committee was obtained prior to sample collection.

Results: Of the 39 eyes, 18 had high-risk pathology. When the group was sub-classified using the IIRC classification, 1/7 Group D eyes and 17/32 Group E eyes had high-risk pathology. Using this classification, we determined the global gene expression patterns from 2 Group D and 7 Group E eyes with differential risk scores.
Based on this categorization, 1027 and 2633 genes were associated with Group E and Group D eyes respectively (p≤0.05 and fold change≥2). When the stringency was raised to fold change>10, the Group E eye with high-risk pathology had 108 unique deregulated transcripts compared to 473 for the Group D eyes without high-risk pathology. Pathway analysis performed with the differentially expressed genes revealed predominant pathways like EGFR signaling, androgen receptor signaling, proteasome degradation and electron transport chain, in the Group E eyes with high-risk pathology. Amongst the most highly deregulated genes, the E2F family, SYK, CD86 and CDC20 were expressed at significantly higher levels in the Group E eyes with high-risk pathology, while RDH12 was most downregulated.

**Conclusions:** Clinical and pathological risk criteria may not always correlate, but a gene expression signature for differential risk groups was discovered. The data illustrate a molecular pattern that correlates with clinical high risk in Rb patients and may provide some novel clues for management.

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**Clinical and pathological risk criteria may not always correlate, but a gene expression signature for differential risk groups was discovered.**

**Effect of Vitrectomy and Silicone Oil on Visual Acuity**

**Program Number:** 3449 **Poster Board Number:** C0260  
**Presentation Time:** 11:00 AM–12:45 PM 
**Iodine-125 Brachytherapy for Large Choroidal Melanomas:** Effect of Vitrectomy and Silicone Oil on Visual Acuity 
**Purpose:** To describe our experience with globe-conserving therapy of large choroidal melanomas with iodine-125 brachytherapy and to compare visual outcomes and complications between patients who underwent brachytherapy alone to those who underwent brachytherapy with vitrectomy and silicone oil for radiation attenuation. We have previously reported the clinical benefit of silicone oil 1000 cs in reducing radiation retinopathy in patients.

**Methods:** Patients diagnosed with a choroidal melanoma and for whom a 23 mm diameter iodine-125 plaque was constructed were identified and retrospectively reviewed. Patients were included who had undergone primary treatment and who had a minimum follow-up of one year. Patient demographics and tumor characteristics were recorded at baseline and at last follow-up visit. Outcomes including tumor control, complications and metastasis were obtained.

**Results:** Thirty-six patients with large choroidal melanoma were treated with a 23 mm custom-designed iodine-125 plaque with an average follow-up of 27.7 months (range 12.3 to 71 months). The average tumor height was 7.43 mm (range 2.0 to 10.95 mm) and average greatest basal diameter was 16.73 mm (range 11.72 to 21.3 mm). Twenty-two were treated with brachytherapy alone, and 14 were treated with brachytherapy in combination with vitrectomy and silicone oil. Thirty-five of 36 eyes (97%) achieved local tumor control at last follow-up. Local treatment failure occurred in two cases (5.6%), with tumor control achieved following repeat brachytherapy in one case, and enucleation for tumor control in the second. There was no case of neovascular glaucoma. Patients achieved 20/40 or better vision in 10% of the plaque group and in 40% of the plaque combined with vitrectomy and silicone oil group (p<0.05). Patients had 20/200 or worse vision in 80% of the plaque group and in 30% of the plaque/Silicone Oil group (p<0.05).

**Conclusions:** In our experience, iodine-125 brachytherapy for large choroidal melanomas is effective at achieving local tumor control with few complications. Furthermore, combining brachytherapy with vitrectomy and silicone oil significantly improves vision over plaque alone. Brachytherapy with vitrectomy and silicone oil may be indicated for globe preservation and maximizing final vision in the treatment of large choroidal melanoma.

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