Complex Ocular Oncology: Evolving Treatments in the absence of clinical trials – 3 decades focused on decreasing treatment related morbidity/mortality

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OBJECTIVE To report strategies for evolving novel treatments in ocular oncology utilizing three decades of integrated care.

PURPOSE The purpose of this study was the evaluate shifting treatment trends at a major ocular oncology service focused on tumor control, anatomic and visual function, and mortality in both uveal melanoma and retinoblastoma patients treated by a single oncology practice (MOOR) over a three decade period. This study evaluated the shift in personalized ocular oncology care to deliver earlier treatment, to avoid enucleation, to minimize systemic toxicity and to use secondary pharmacotherapy to improve outcomes for the most common primary adult and pediatric ocular malignancy.

METHODS An IRB approved, retrospective review of all patients undergoing treatment for primary posterior uveal melanoma over three decades. 2,375 primary posterior uveal melanoma patients and 398 primary retinoblastoma patients were included in this analysis. Patient demographics, tumor size, primary treatment, adjunctive treatment, secondary surgery, metastasis and mortality were recorded for all patients. Outcomes analysis utilized treatment intervals from: 1991 – 2001, 2002 – 2011, and 2012 – 2017 and stratified tumors by size from small (<2.5mm), medium (2.5 – 10mm), and large (>10 mm apical height OR >16mm base) for uveal melanoma and by RE classification for retinoblastoma.

RESULTS During this study for uveal melanoma patients, treatment size at time of treatment decreased ($p<.04$), patient melanoma specific mortality decreased ($p<.02$),

secondary enucleation rates decreased (p<.03), and final median visual acuity increased (p<.05). By the third treatment interval virtually all patients were treated with either brachytherapy of radiosparing MIVS surgical management. By the concluding interval of analysis, no patient required secondary enucleation. Mortality rates declined by tumor size over the treatment intervals with final 5 year Kaplan-Meier melanoma specific mortality rates at 5 years of <1% for small tumors, 6.2% for medium tumors, and 19.7% for large tumors. Secondary 5 year enucleation rates declined from 6% to less than 1% over the study window. Mean 5 year VA improved from 1991-2001 through 2012-2017 from 20/100 to 20/62 highlighting the response to intravitreal pharmacotherapy. From 1991 to 2010 retinoblastoma children were treated with systemic multi-drug chemotherapy with Carboplatin, Vincristine, Etoposide with/without Cyclosporine was the primary therapy. Typically, advanced eyes were scheduled for 9 cycles of planned systemic chemotherapy. From 2011 to the present, eyes were treated with intra-arterial chemotherapy if vascular access was possible. If vascular access was not available, bridging systemic chemotherapy as noted above was utilized followed by transition to IAC. IAC eyes were treated with 6 cycles of single drug high dose Melphalan. If tumor response was ongoing but tumor activity was present additional IAC was performed until tumor stability was documented. In eyes unresponsive to systemic chemotherapy/IAC all eyes underwent enucleation. One child treated with primary systemic chemotherapy and one child treated with primary IAC both with Group D advanced retinoblastoma developed metastatic disease and died (1/97, 1.03%/1/275, 0.37% Systemic Chemotherapy). Secondary enucleation rates declined from 1991 to 2010 and declined further from 2011 to present (approximately 3%, p<.01).

CONCLUSION Personalized treatment in ocular oncology has incorporated earlier tumor treatment, avoidance of enucleation, and integration of molecular genomics. Retinoblastoma treatments have focused on decreased treatment related morbidity, decreasing enucleation while maintaining excellent survival. These advances have come from ocular oncology centers, incorporating advanced therapeutics, without the aid of randomized clinical trials. This evolution in care demands outstanding, and ongoing, focus by each individual center to evaluate shifting treatments with real-time analysis.

HUMAN RESEARCH Yes: Approved by institutional review board

Update from an Ongoing Phase 1b/2 Open-Label Clinical Trial Evaluating the Safety and Efficacy of AU-011 for the Treatment of Choroidal Melanoma

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OBJECTIVE To evaluate the safety and efficacy of AU-011 in a dose escalation and expansion trial

PURPOSE Most small choroidal melanomas (CM) are treated with radiotherapy which is associated with several adverse effects including vision loss. AU-011 is a novel, potentially vision-sparing, targeted investigational therapy being developed for the treatment of CM with a Phase 1b/2 trial ongoing and Phase 3 studies planned. Interim results of the Phase 1b/2 trial will be presented.

METHODS Subjects with CM with tumor thickness from 1.2 - 3.4 mm and largest basal diameter ≤ 16 mm received intravitreal administration of a viral-like particle bioconjugate (AU-011) at doses of 20 µg, 40 µg, or 80 µg followed by light-activation with a 689 nm laser

at a fluence of 50 J/cm2. Regimens consisting of 1, 2 or 3 weekly treatments with AU-011 each followed by 1 or 2 laser applications have been evaluated in 8 escalation cohorts and 1st expansion. Enrollment is nearing completion in the 2ndexpansion with subjects receiving two cycles of three weekly treatments with 80 µg/2 laser administrations separated by 12 weeks.

RESULTS 50 subjects have been treated with up to 3 weekly treatments of 80 µg/2 laser administrations. Interim results show local tumor control in 33/50 (66%) subjects (23/29 [79%] at therapeutic dose) and maintenance of visual acuity in 46/50 (92%) subjects (27/29 [93%] at therapeutic dose) with up to 24 months follow up. Linear regression was used to estimate tumor growth rates using tumor thickness measurements before and after treatment in subjects with historical documented growth (n=19). Tumor control was seen in 15/19 subjects and the post-treatment growth rate was significantly reduced compared to their historical growth rate (p=0.0056; paired t-test). There has been one treatment-related SAE of severe vision loss. Expected AEs related to treatment including intraocular inflammation and increased IOP were clinically manageable.

CONCLUSION Preliminary safety and efficacy of AU-011 has been observed in this ongoing Phase 1b/2 trial. The therapy was well tolerated with maintenance of vision and tumor control in the majority of subjects. Phase 3 studies with sham control are planned in subjects with documented growth to confirm the safety and efficacy of AU-011 for treating small CM and high risk indeterminate lesions.

HUMAN RESEARCH Yes: Approved by institutional review board