Retinoblastoma is the most common primary intraocular malignancy of childhood affecting approximately 5,000 to 8,000 children per year worldwide. Although regional variations in the incidence of retinoblastoma exist, it is estimated that 80% of children with retinoblastoma reside in developing countries [1]. There is little question that the primary aim in the treatment of retinoblastoma should be preservation of life, with maintenance of the eye and vision as secondary and tertiary objectives. However, new treatment strategies targeting in particular, the secondary objective of saving the eye, are gaining wide acceptance in spite of scant evidence that preservation of vision is enhanced. Additionally, mounting evidence that life-threatening side effects and the potential for metastasis may in fact, compromise the primary aim of treatment. Ocular pathology plays a pivotal role in providing the careful assessment of outcomes necessary for defining and refining these new treatments.

Detecting High-Risk Features: Multiple investigators have attempted to define the risk of attempted ocular salvage. Zhao et al. eloquently addressed this question in their 2011 study [2]. The authors showed that attempted salvage of eyes with the most advanced intraocular retinoblastoma (Internal Classification Group E) down-staged subsequent pathology, masking high risk features, and in turn, increased the incident of death from metastases due to inappropriate surveillance and adjuvant therapy. Some authors have argued that magnetic resonance imaging (MRI) may detect high-risk features such as massive choroidal invasion and post-laminar optic nerve extension [3]. However, clinical pathologic correlations of primarily enucleated eyes have failed to show a significant correlation between pathology and MRI [4,5]. Additional studies have correlated high-risk pathology features with International Classification of Retinoblastoma Grouping. Group D eyes were found to have a 10% risk of harboring at least one high-risk feature while 50% of Group E eyes had at least one high-risk pathologic feature [6]. Pathology remains the gold standard for defining the risk and need for adjuvant therapy in the treatment of intraocular retinoblastoma.

External Beam Radiation and Systemic Chemotherapy: While rare tumors and orphan diseases have historically relied upon adaptation of existing therapeutic measures, their accepted adaptation requires vetting of benefit and toxicities. No better example exists than that of the use of external beam radiation for the treatment of retinoblastoma. Introduced in the early part of the twentieth century, radiation for the then termed, “glioma retinae,” showed efficacy in tumor control, preserving eyes, and vision [7]. Ocular and orbital complications were quickly apparent but only decades later were the risks of secondary cancers appreciated [8]. In the 1990’s, primary systemic triple agent chemotherapy (carboplatin, vincristine and etoposide) moved to the forefront in the treatment of intraocular retinoblastoma based on the successful treatment of metastatic disease and need to avoid or at least delay external beam radiation in children less than 1 year of age [9]. Improved ocular survival rates results were quickly reported but long-term toxicities of secondary acute myelogenous leukemia and ototoxicity were slow to be recognized [10,11].

Super Selective Intra-Arteriole Chemotherapy (SSIOAC): Our studies of another technique adapted for the treatment of retinoblastoma, SSIOAC, raise concerns of possible short and long-term toxicities. SSIOAC has gained increased popularity as both primary and secondary treatment of retinoblastoma since initial reports of its use in 2008 [12]. Adapted from Kaneko’s balloon assisted intra-carotid infusions, SSIOAC delivers a highly concentrated dose of chemotherapy, typically melphalan, to the eye in hopes of mitigating systemic exposure [13]. Tumor response has been dramatic but adverse ocular and orbital vascular toxicities have been reported. A non-human primate model using adult male Rhesus macaques has documented these adverse ocular events with real time fundus photography [14]. Pathologic review of these treated eyes and orbits have shown an array of vascular toxicities; occlusion of the retinal, choroidal and short posterior ciliary arteries as well as intimal hyperplasia and dissection of the ophthalmic artery [15,16]. These findings are in keeping with in vitro cell assays that suggest a complex interaction between drug concentration, drug delivery, inflammatory mediators, leukostasis, and formation of particulates, with an end result of endothelial cell inflammation and apoptosis [17]. Given the highly compromised vasculature, long-term preservation of vision after SSIOAC appears threatened. These documented ocular pathologies resulting from SSIOAC suggest strategies should be pursued for future refinement and mitigation of toxicities associated with this otherwise promising treatment.

Molecular Pathway Targeting: Ideally, what is needed for the treatment of retinoblastoma is targeted therapy that disrupts aberrant molecular pathways. Identifying potential targets had required the study of multiple tumor cell lines, using either DNA/ RNA extraction or more sophisticated techniques such as orthotopic xenografts. Laurie et al. first reported inactivation of the p53 pathway in retinoblastoma by over expression of MDMX [18]. Brennan et al. then showed selective inhibition of MDMX with Nutilin-3a with improved outcomes in mice with human orthotopic xenografts [19]. More recently, the pediatric cancer genome project has shown the retinoblastoma genome to be very stable in comparison to other cancers. The stability exists over time, being present in freshly harvested tumor as well as in tumor cells harvested after multiple passages in orthotopic xenografts. Further investigation showed over-expression of the spleen tyrosine kinase protein (SYK), an epigenetic regulator [20]. Immunohistochemistry showed robust expression of SYK in primary enucleated tumors. SYK expression not only provides a useful marker for retinoblastoma, SYK inhibition now presents a

**Ocular Pathology: Essential for Defining and Refining the Treatment of Retinoblastoma**

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potential target therapy. Judicious use of pathologic specimens and sophisticated molecular techniques has provided new insights into the biology of retinoblastoma as well as promising targeted therapy for this orphan disease.

Furthering our understanding of tumor biology is the means by which we will improve lives and outcomes in our retinoblastoma patients. Ocular pathology and pathologist are as integral to this process as are clinicians and translation researchers. In collaboration, we define and refine our treatment of retinoblastoma.

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