Rabbit Model of Intra-arterial Chemotherapy: Technique, Vascular Variations, Pharmacokinetics, and Toxicities

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Purpose: To describe a novel rabbit model of intra-arterial chemotherapy (IAC), determine anatomic variations in ocular blood supply, and determine the pharmacokinetics, tissue drug levels, and systemic and ocular toxicities of IAC melphalan.

Methods: Ocular vascular supply was determined angiographically in 79 eyes of 47 3.0kg-New Zealand white rabbits. The dominant ophthalmic artery (OA) of each eye was selectively catheterized. Melphalan 0.4mg/mL (up to 1.2mg/kg) was infused in pulsatile fashion. For pharmacokinetic studies, 18 rabbits were sacrificed at serial time-points. Retina, bilateral vitreous, and blood were collected.

Toxicity was assessed by fluorescein angiography, electroretinography, and histopathology, prior to and 5-weeks post-treatment. Complete blood counts were obtained weekly.

Results: The OA was successfully catheterized for 79/79(100%) eyes in 47/47(100%) rabbits. Melphalan was delivered successfully in 31/31(100%) eyes. External OA-dominant vascular variation was present in >75% of eyes. In treated eyes, maximum melphalan concentration (C_max) in retina was 4.95µM (30-minutes post-infusion) vitreous C_max was 2.24µM (1-hour), and areas-under-the-curve (AUC⁰→∞) were 5.26µM*hr for retina and 4.19µM*hr for vitreous. Peripheral blood C_max was 1.04µM. Drug half-life was ~1 hour. Treated eye vitreous C_max was >100-fold higher, and AUC⁰→∞ was ~50-fold higher, than untreated eye. No angiographic or histopathologic evidence of vascular occlusion, emboli, or retinal damage were seen, even with 1.2mg/kg melphalan. Electroretinographic reductions were not seen. With 0.8-1.2mg/kg melphalan, transient neutropenia occurred at 1-week.

Conclusions: This is the first small animal model of IAC. IAC melphalan delivery in rabbits leads to excellent ocular penetration and pharmacokinetics, without significant ocular, vascular, or systemic toxicities.