Aus der Klinik für Augenheilkunde
der Medizinischen Fakultät der Charité – Universitätsmedizin Berlin

DISSERTATION

Coulomb controlled Iontophoresis of Carboplatin in the treatment of the transgenic murine retinoblastoma

(Coulomb-kontrollierte Iontophorese von Carboplatin zur Behandlung des Retinoblastoms am transgenetischen Mausmodell)

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9. CURRICULUM VITAE

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„Mein Lebenslauf wird aus Datenschutzgründen in der elektronischen Version meiner Arbeit nicht mit veröffentlicht."

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Eidesstattliche Erklärung

Hiermit bescheinige ich, daß die Dissertation von mir selbst und ohne die (unzulässige) Hilfe Dritter verfaßt wurde, auch in Teilen keine Kopie anderer Arbeiten darstellt und die benutzten Hilfsmittel sowie die Literatur vollständig angegeben sind.

Monika Voigt

Objective: Retinoblastoma is the most common intraocular malignancy in children. Recently, the management of retinoblastoma has evolved away from radical aggressive treatments such as enucleation and external beam radiation, towards more focal, conservative treatments or moderate, combined treatment modalities. The aim of this study was to characterize the pharmacokinetics and toxicity of systemic versus focal subconjunctival and transscleral Coulomb controlled iontophoresis (CCI) of carboplatin administration in the rabbit eye. The next step was to evaluate the efficacy and the dose response of transcorneoscleral Coulomb controlled iontophoresis (CCI) of carboplatin in the treatment of murine transgenic hereditary retinoblastoma.

Methods: Pharmacological distribution of carboplatin was examined in New Zealand White (NZW) rabbits following a single intravenous infusion of carboplatin (18.7mg/kg body weight), a single subconjunctival carboplatin injection (5.0mg/400µl), or a single application of carboplatin delivered with CCI at 5mA/cm^2 for 20min treatment duration (14mg/ml carboplatin solution). Following each treatment, animals were euthanized and eyes were obtained at either 1, 2, 6 or 24hrs post treatment. Six animals per time point were treated to ensure statistical significance. Right eyes were treated, left eyes served as controls. Atomic absorption spectroscopy analysis was used to determine the carboplatin levels in the blood plasma and ocular tissues.

Twelve adult NZW were used for histopathological and functional toxicity evaluation. The rabbits underwent 6 serial iontophoretic treatments (20min at 2.5mA) of either balanced salt solution (BSS) or carboplatin (14mg/ml) administered to the right eye at 72-hour intervals. The left eyes served as untreated controls. ERGs were recorded prior to the initial treatment, than at 48hrs after the 2nd treatment, and 4 weeks post final treatment. All eyes were examined clinically following each CCI application.

Fifty-four 6 weeks old SV-40 transgenic mice underwent six, serial transcorneoscleral iontophoretic treatments (2.57mA/cm^2, 5min) with carboplatin. Forty-four animals received carboplatin treatments at concentrations of 1.4, 7.0, 10.0, or 14mg/ml with or without current. Ten control mice underwent a treatment with balanced salt solution. Coulomb controlled iontophoresis treatment parameters include current density and charge application times were evaluated in 8 animals. Experimental and control eyes were examined for toxicity preceding each application. All eyes were obtained at 16 weeks of age for histopathological evaluation.

Results: Determination of carboplatin concentrations via atomic absorption spectroscopy in the retina, choroid, vitreous humor, and optic nerve following subconjunctival injection and iontophoretic carboplatin delivery revealed significantly higher levels than those achieved with systemic administration. Peak levels of carboplatin in the retina were determined to be

53.68ng/mg following subconjunctival, 38.0ng/mg post CCI-delivery and 14ng/mg after intravenous administration at 1hour post treatment. Concentrations in the vitreous humor following treatments peaked at differing times: 1hr post subconjunctival injection (4560ng/ml), 6hrs post CCI delivery (1955ng/ml) and 6hrs post intravenous delivery (1220ng/ml). Carboplatin concentrations in the blood plasma were found to be significantly higher following intravenous delivery with a concentration of 6222ng/ml at 1hour, compared to concentration of 182ng/ml and 261ng/ml at 1hour for subconjunctival and iontophoretic drug delivery.

Light microscopy showed no histopathologic alterations in eyes treated with single or repetitive CCI carboplatin. ERGs revealed no depression in the a- or b-wave amplitude or alteration in the implicit times of the treated eyes.

A dose–dependent inhibition of intraocular tumor was observed following repetitive iontophoretic treatment. None of the experimental eyes treated at carboplatin concentrations of 1.4mg/ml demonstrated complete tumor control. At concentrations of 7mg/ml the treated eyes exhibited tumor control of 50 %. All eyes treated with 14mg/ml showed complete tumor control. No corneal toxicity was observed in eyes treated at carboplatin concentrations less than 10mg/ml. At 14mg/ml all of the treated eyes revealed corneal damage.

Conclusions: Focal administration of carboplatin utilizing subconjunctival or CCI, effectively transmits this chemotherapeutic drug into the target tissues of retina, choroid, vitreous and optic nerve. This data suggests local carboplatin delivery may be effective and well tolerated in the treatment of human retinoblastoma by increasing the intra-orbital carboplatin concentration while decreasing systemic exposure to this cytotoxic drug.

Furthermore repetitive CCI administration demonstrated no signs of ocular toxicity and may present an alternative method to repetitive intravenous carboplatin administration.

Transcorneoscleral Coulomb controlled iontophoretic delivery of carboplatin safely and effectively controls intraocular retinoblastoma in a dose dependent manner in this murine model of retinoblastoma. Topical non-invasive ocular iontophoretic administration of carboplatin chemotherapy may be advantageous in the treatment of intraocular pediatric retinoblastoma in comparison to systemically applied chemotherapy.