2. AIM OF THE STUDY

A variety of different treatment modalities for the management of retinoblastoma exists as already demonstrated previously. Different factors, like tumor size and extent, vitreous seeding, site of involvement and patients' systemic status influence the suitability of each technique, but furthermore each treatment is marked by its inherent side effects.

Complications associated with systemic chemotherapy, such as significant morbidity and potential mortality caused by drug-related toxicity including induced neutropenia and bone marrow suppression, ototoxicity, nephrotoxicity, and CNS toxicity are severe problems with this treatment protocol [184-188]. Despite the improved therapeutic index achieved with carboplatin chemotherapy, systemic chemotherapy alone does not result in complete tumor control in most patients with retinoblastoma. This may be due to the effect of chemoresistance, which decreases the efficacy of the drug. It has been hypothesized that incomplete tumor control may be associated with inadequate carboplatin penetration into the ocular tissues, non-tumoricidal intracellular levels within the tumor cells, or the selection of chemotherapeutic resistant tumor cell lines [189]. Enhanced intracellular carboplatin levels within the target tumor tissue is believed to be associated with increased tumor control and has prompted recent investigations of high dose systemic chemotherapy protocols in human retinoblastoma.

As a result, local chemotherapy application has received increased interest, as it offers the capability of minimizing systemic exposure while obtaining effective dosages within the eye. Delivery techniques such as periorbital and subconjunctival drug administration were studied and their efficacy for tumor control in animal models have been proven and published [190-194].

Our laboratory sought to develop a system of chemotherapy administration capable of obtaining therapeutic drug concentrations in the eye while not only reducing systemic exposure but also minimizing local orbital and extraorbital toxicity. Current Controlled Iontophoresis (CCI) offers a defined, selective, and controlled drug administration limited to the globe that is simple and noninvasive. Iontophoresis, the transfer of charged drug molecules across tissues through an electric field, has already been demonstrated to enhance delivery of various drugs into the anterior and posterior segments of the eye [29].

The management of retinoblastomas is a complex system of different treatment modalities. Integrating CCI of carboplatin into this system may offer a more selective, potentially safer, and more effective non-invasive transocular tumor control method. In this study we wanted to analyze the efficacy of CCI to deliver therapeutic drug concentrations of carboplatin to the eye in comparison to intravenous and subconjunctival administration. Therefore the distribution pattern

of carboplatin in the different ocular tissues was evaluated, while carboplatin was administered by intravenous, subconjunctival and CCI routes to rabbits.

Furthermore we investigated the safety of repetitive transscleral CCI applications of carboplatin, simulating clinical chemotherapy conditions. Finally the efficacy of iontophoretic delivery of carboplatin was studied in the treatment of murine transgenic retinoblastoma. The ability to focally deliver chemotherapy, while maintaining local tumor control, has the potential to impact significantly the management of human retinoblastoma.