Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/survophthal

Therapeutic review

Local chemotherapeutic agents for the treatment of ocular malignancies

Bruno F. Fernandes, MD, PhD, Katerina Nikolitch, MD, James Coates, Gustavo Novais, MD, PhD, Alexandre Odashiro, MD, PhD, Patricia P. Odashiro, MD, PhD, Rubens N. Belfort, MD, PhD, Miguel N. Burnier Jr., MD, PhD, FRCSC*

Department of Ophthalmology and Pathology, The McGill University Health Center, and Henry C. Witelson Ocular Pathology Laboratory, Montreal, Canada

ARTICLE INFO

Article history:
Received 19 April 2012
Received in revised form
24 January 2013
Accepted 29 January 2013
Steven Teich, Editor

Keywords:
mytomicin
carboplatin
interferon
PAM
melanoma
retinoblastoma
carcinoma
conjunctiva
PAM
CIN

ABSTRACT

We critically analyze available peer-reviewed literature, including clinical trials and case reports, on local ocular cancer treatments. Recent innovations in many areas of ocular oncology have introduced promising new therapies, but, for the most part, the optimal treatment of ocular malignancies remains elusive.

1. Introduction

Ocular oncology, a specialty that deals with tumors of the eye and ocular adnexae, has undergone dramatic changes over the past few years. Albeit rare, malignancies are the major life-threatening ocular conditions. The development of new diagnostic tools allowing early diagnosis and treatment translates into improved survival rates for some cancers.[130] Nevertheless, the ocular oncologist still relies on the basic triad of oncology therapy: radiation, surgical resection, and chemotherapy.

A better understanding of the intricacies of each tumor allows the use of more conservative therapeutic approaches. That way, disfiguring surgical procedures such as

* Corresponding author: Bruno F. Fernandes, MD, PhD, 3775 University Street, Room 216, Montreal, Quebec, Canada H3A-2B4.
E-mail address: bruno.mtl@gmail.com (B.F. Fernandes).

0039-6257/$ – see front matter
http://dx.doi.org/10.1016/j.survophthal.2013.01.003

exenteration are far less often performed, especially because they fail to lower tumor-related deaths.[147] Understanding the importance of free margins and the use of no-touch techniques for the resection of ocular surface tumors has further decreased recurrence rates.[153]

Radiotherapy has also evolved over the years. New delivery methods are far more accurate, allowing higher doses to the tumor and less "spillage" to adjacent tissues. Consequently, patients enjoy higher rates of local tumor control with fewer radiation-induced complications, which are often associated with significant visual loss.

Lastly, the use of chemotherapy has also evolved. Systemic chemotherapy is still useful for the treatment of some cancers, but there is a trend towards the local use of such medications in order to deliver higher doses to the tumor and avoid systemic toxicity. We review the pertinent available literature concerning the use of local chemotherapy for the treatment of ocular malignancies.

2. Rationale for local chemotherapy

Intraocular tumors are difficult to treat with systemic chemotherapy because of the blood–retinal barrier and the small size of the eye. In order to achieve therapeutic doses inside the eye, high doses of the drug have to be injected intravenously. The drug is dispersed over the entire body to target an organ that represents only 0.0001% of the total body weight (considering the average weight of a human eye of 8 g in a 75 kg individual). Moreover, the tumor mass usually is even smaller.

The eye is perfectly suited for the local delivery of chemotherapeutic agents. In the case of intraocular tumors, the injection of the agent into the eye allows the achievement of high doses and decreases the risk of associated systemic side effects. For ocular surface tumors, the use of local chemotherapy is even more appealing, given the direct access to the tumor mass. Some may be conveniently delivered in the form of eye drops applied directly to the surface of the tumor and with limited systemic absorption.

3. Treatment of intraocular tumors

3.1. *Carboplatin*

The use of locally delivered carboplatin for the treatment of ocular tumors is still controversial. Ongoing studies are evaluating the efficacy of various drug delivery modes, as well as the toxicity associated with various schedules, doses, and techniques of delivery. Although early results seemed promising, concerns about its toxicity and extraocular dissemination may limit its use in the treatment of retinoblastoma.

3.1.1. *Mechanism of action*

Carboplatin is a platinum(II) complex with two ammonia groups in the *cis* position and a cyclobutane dicarboxylate moiety. Its exact mechanism of action is yet to be conclusively determined, although it has been postulated to be similar to that of another platinum analogue, cisplatin.[9,45,56,93] Its primary function appears to be that of a non-classical alkylating agent with its major cytotoxic target being the DNA.[56,93] Like cisplatin, carboplatin binds covalently with the N7 of guanine and adenine in double-stranded DNA following an initial aquation reaction displacing the cyclobutane moiety.[56,92] The result of this interaction is the formation of both intrastrand and interstrand DNA cross-links. Although the relative importance of these in the antineoplastic effects of carboplatin has not been clearly determined, interstrand cross-linking seems to correlate well with carboplatin cytotoxicity.[9] The DNA–platinum adducts are stable, covalent bonds that do not disassociate easily and play a role in inhibiting DNA synthesis and transcription, thus leading to cell death.

3.1.2. *Drug delivery*

Intravitreal injection of carboplatin was initially attempted in rabbits in the 1980s.[190] Later, with the creation of the retinoblastoma model in the transgenic mouse,[114] experimental studies used this method to investigate its efficacy in tumor regression, as well as potential ocular toxicity.[63,104] Because of concerns about extraocular dissemination, this approach has not gained wide acceptance in human trials.[71,105]

Subtenon and subconjunctival injections are also common in animal studies and have been performed without significant side effects in mice[21,66,105,174] and rabbits.[65] In humans, they were used in only a few studies and have been associated with various side effects, some of which may be related to the injection technique, as well as to the rapid dispersal of the drug.[7,91,102,139,174] Recent attempts have been made to decrease side effects by delivering carboplatin in fibrin sealant, a human protein–derived biodegradable surgical adhesive, rather than in the usual aqueous medium.[96,120,156,174] With this approach, periocular side effects are still dependent on the dose of carboplatin administered, but it appears that fibrin sealant may concentrate the carboplatin on a small area of the sclera, thereby minimizing systemic and periocular effects.[96]

Hayden et al[64,65] described local delivery of carboplatin by Coulomb-controlled iontophoresis (CCI) in rabbits[65] and $LH_{BETA}T_{AG}$ mice,[64] using custom-made transscleral coulomb applicators. In the former study the authors compared the pharmacokinetics and toxicity of six serial local applications of carboplatin delivered either through CCI (using 14 mg/mL of carboplatin and 2.5 mA/cm^2 of current for 20 minutes) or subconjunctival injection (5.0 mg/400 μL). No corneal, conjunctival, or sclera toxicity was detected in either group; the peak levels of carboplatin in both retina and choroid were higher when the drug was delivered via subconjunctival injection than with CCI, however. In the latter study they reported corneal epithelial damage at current densities above 5.14 mA/cm^2, regardless of treatment duration, and no toxicity at lower current densities and treatment duration between 2 and 5 minutes. At carboplatin concentrations above 14 mg/mL, 100% of the study eyes exhibited corneal toxicity, with phthisis in some eyes, with no toxicity at concentrations below 7 mg/mL.

3.1.3. *Clinical applications*

3.1.3.1. Retinoblastoma. Locally delivered carboplatin in the treatment of retinoblastoma in human eyes is still not