

The Role of Periocular Carboplatin in Treatment of Advanced Intraocular Retinoblastoma

Masood Naseripour, MD,¹ Siamak AkbarZadeh, MD²
Ali Ahadian, MD,³ Parvaneh Vosough, MD⁴

Abstract

Purpose: To evaluate the results of combined chemotherapy and periocular carboplatin injection to control advanced intraocular retinoblastoma (Rb).

Methods: In this prospective interventional case-series, we included 8 eyes of 8 patients with advanced intraocular Rb (group C or D in International Intraocular Retinoblastoma Classification, IIRC). In these patients, periocular carboplatin was injected as a primary adjuvant therapy combined with chemotherapy (VEC regimen) or as a secondary treatment in patients who had recurrent disease or did not respond to primary chemotherapy and local modalities. All patients were examined under anesthesia (EUA) and fundus photography was done by Ret-cam before treatment. Fifteen milligrams of carboplatin was injected into subconjunctival or subtenon space in 3-4 weeks interval.

Results: Eight eyes of eight patients were enrolled. Five patients were male and three patients were female. Mean age of patients at the time of treatment was 34 months and the mean duration between initial presentation of Rb and beginning of treatment was 7.5 months. Mean injection of periocular carboplatin in each eye was 3.1 times. Past medical history in our patients before starting of this treatment included: External Beam Radiotherapy (EBRT) in 3 eyes, cryotherapy in 4 eyes, transpupillary thermotherapy (TTT) in 4 eyes and brachytherapy in 2 eyes. Four eyes were in group C and four eyes were in group D. In 3 patients carboplatin was injected as primary treatment and in five patients it was injected for tumor recurrence following initial treatment failure or relapse. Three patients had vitreous, one had sub-retinal and remaining four had both vitreous and sub-retinal seeding. The degree of seeding was low in two patients, moderate in two patients and severe in four patients. At the end of study, tumor was regressed in six eyes (75%), relapsed in one (12.5%) and recurred in another (12.5%). In both eyes with relapsed and recurrent tumors, enucleation was done.

Conclusion: Combined chemotherapy and periocular carboplatin injection as well as focal treatment may be an effective method to control advanced intraocular Rb.

Keywords: retinoblastoma, intraocular tumor, systemic chemotherapy, carboplatin

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1. Associate Prof. of Ophthalmology, Eye Research Center, Rasoul Akram Hospital, Medical Sciences/University of Iran
 2. Assistant Prof. of Ophthalmology, Rasoul Akram Hospital, Medical Sciences/University of Hamedan
 3. General Practitioner, Eye Research Center, Rasoul Akram Hospital, Medical Sciences/University of Iran
 4. Professor of Pediatric Oncology, Ali-Asghar Hospital, Medical Sciences/University of Iran

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Correspondence to:
Masood Naseripour, MD
Eye Research Center,
Rasoul Akram Hospital, Tehran
Tel:+98 21 66509162
Email: masoodnp@yahoo.com

Introduction

Retinoblastoma (Rb) is the most common primary intraocular tumor in childhood, with mean annual incidence of 10.9 per one million for children under 5 years old¹; which is nearly equal to incidence of one case in 18000 live births.² Although new chemotherapy agents (Vincristine, Etoposide, Carboplatin as VEC protocol) has been accepted as mainstay of treatment for Rb since 1996, Wilson and colleagues showed that chemotherapy alone does not ensure a cure for Rb and adjuvant focal treatments such as cryotherapy, thermotherapy, photocoagulation by laser and plaque radiotherapy are needed to control the disease.³

Results of combined chemotherapy and focal treatments based on both Reese-Ellsworth (RE)⁴ and international intraocular Rb classification (IIRC)⁵ showed that although the chance of EBRT and enucleation are low in less advanced groups (I-IV in RE classification and A and B groups in IIRC), but advanced cases of the disease particularly those with intravitreal or subretinal seeds, need more intervention. These modalities mainly emphasize on different chemotherapeutic agents,⁶ reversing of multi-drug resistance by cyclosporine,⁷ increasing of intraocular level of chemotherapeutic agents by periocular carboplatin injection^{5,8} and using high doses VEC protocol instead of standard dose⁹ and sustained-release implant for chemotherapeutic agents.

In this study, we evaluated the results of combined chemotherapy and focal treatments in association with periocular carboplatin injection in treatment of advanced intraocular retinoblastoma (groups C and D in IIRC or group V in RE classification).

Methods

During 5-year period from 2002 to 2006 in a prospective case-series, we enrolled eight eyes of eight children with C and D group of Rb (Group V in RE classification) in the Rasoul Akram Hospital in this study. In 3 patients periocular injection was done as primary treatment combined with systemic chemotherapy and focal treatment in less advanced eye, because the other eye was candidate for enucleation. In 5 other eyes, periocular injection was done for recurrent

disease or an incomplete response to primary systemic chemotherapy and adjuvant treatment.

All clinical and demographic data of patients were recorded in designed fellow sheets. Fundus photographs for all patients using Ret Cam (Massie industries, Dublin, CA) were taken. Examinations under anesthesia (EUA) during the period of chemotherapy by VEC protocol (using 0.05 mg/kg vincristine, 5mg/kg Etoposide and 18.6 mg carboplatin) were planned for all patients.

For periocular injections 15 mg carboplatin was injected subconjunctivally during the first 3 years of the study and then we injected 15 mg carboplatin in subtenon space, 8 mm from limbus between rectus muscles in the nearest quadrant to the vitreous seeding location in group C or at the infratemporal quadrant in group D eyes. Carboplatin concentration was 10 mg/ml, so for each patient, total volume of 1.5 cc was injected by blunt needle after local opening of conjunctivae and tenon from 8 mm of the limbus. The needle was pointed toward posterior over the sclera and deeply injected. Severity of seeding described as very low for 1-10, low for 10-20, moderate for 20-50 and severe for more than 50 seeds.

Before beginning the chemotherapy, informed consent to participate in the study was obtained from the parents of the patients. Complete description of treatment protocol and patient's prognosis was explained as well. Periocular injection was continued every 4-6 weeks till the disease progression was controlled.

Depending to the other eye condition, eyes failing to respond to this conservative method were enucleated or underwent EBRT.

Results

Five cases (62.5%) were male and 3 cases (37.5%) were female. Except one case who had unilateral Rb in group C; other 7 cases (87.5%) had bilateral Rb. Mean age at diagnosis was 34 months and the time period between presenting symptoms and starting the treatment was 7.5 months.

Mean injection session in each eye was 3.14 (1-4 times). Three patients had a history of EBRT on the other eye, 4 patients had a history of cryotherapy, 4 patients had transpupillary thermotherapy (TTT) and 2

cases had a history of brachytherapy in the same eye.

In average, each patient had been received 9 cycles of chemotherapy with VEC protocol. Four eyes were in group C and 4 eyes were in group D. Three patients had vitreous, one had subretinal and remaining four had both vitreous and subretinal seeding. The degree of seeding was low in two patients, moderate in two patients and severe in four patients.

Mean follow up period was 30 months (18-56 months). At the end of the study, the disease was completely regressed in 6 cases (75%); 2 patients were enucleated because of relapse of the disease in one patients and recurrent diffuse vitreous seeding in spite of primary regression in another patient. The disease process was controlled in all eyes of group C. Both eyes, which underwent enucleation, were in group D. Significant conjunctival scar combined with local symblepharon and ocular motility restriction were occurred in 3 patients who had got subconjunctival periocular injection. One of these patients underwent enucleation.

In most of the cases, some levels of orbital fat atrophy were seen. Transient side effects like redness, chemosis and mild palpebral edema that occurred in all patients, were controlled by using topical steroids and cold compression in few days after injection.

Discussion

Results of this study showed that periocular injection of carboplatin combined with systemic chemotherapy and focal treatment can increase the success rate of the treatment. In recent years several reports has been published regarding the effectiveness of focal carboplatin combined with chemotherapy in patients with advanced retinoblastoma.

One study on mice infected by Rb induced virus showed that subconjunctival carboplatin was effective in Rb treatment.¹¹ Mendelson and colleagues study revealed that vitreous concentration of carboplatin in monkeys following periocular injection was 7 to 9 times more than after intravenous injection of

carboplatin; whereas this concentration in anterior chamber was 30% of intravenous injection; so they calculated that focal injection of carboplatin could be a good treatment of choice in cases of seeding, without increasing the risk of anterior segment toxicity.¹²

Moreover, some other studies have shown that subconjunctival⁸ and intravitreal¹³ carboplatin injections can be effective in treatment of advanced intraocular Rb.

Our previous study on patients with Rb¹⁴ showed that the success rate of systemic chemotherapy in combination with focal therapy in groups C and D (Group V in RE classification) was about 21.5%. Despite of using EBRT, 50% of the patients underwent enucleation finally. These results is comparable with Shields and colleagues⁴ results in which 53% of cases underwent enucleation in spite of EBRT; whereas in the present study only 25% of patients using chemotherapy and focal treatment in combination with repetitive periocular carboplatin injections underwent enucleation.

In this study, the disease process was controlled in 75% of the cases; which is compatible with the results of Mulvihill and colleagues¹⁵ study in a similar study on 12 eyes of 10 patients with progressive retinoblastoma with 66.5% success rate of controlling the tumor growth while 33.5% were enucleated.

Although in Mulvihill study most of the patients had noticeable soft orbital tissue fibrosis, this complication happened only in 3 patients of our study and in the other cases soft tissue fibrosis was mild to moderate with no severe eye movement restriction.

Conclusion

In spite of limitation in sample size in this study, it seems that using systemic chemotherapy and focal treatment combined with periocular injection of carboplatin can be an effective way to treat advanced intraocular retinoblastoma. Although, future randomized clinical trials with enough sample size can better reveal the possible risks and benefits of this method.

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