Subtenon Carboplatin in the Management of Intraocular Retinoblastoma

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ABSTRACT

Purpose: To evaluate the efficacy of adjuvant subtenon carboplatin in the management of intraocular retinoblastoma.

Methods: This study was conducted as a randomized, double-masked clinical trial. A diagnosis of intraocular retinoblastoma was made based on clinical examination, ultrasonography and orbital CT-scanning. The greatest basal dimension of the tumors was estimated in disc diameter (DD) by indirect ophthalmoscopy. Tumor thickness was determined by ultrasonography. Each eye was assigned to one of 10 blocks based on tumor stage (Reese-Ellsworth classification) and randomly received systemic chemotherapy alone (control group) or systemic chemotherapy plus 20mg subtenon carboplatin (case group). Indirect laser photocoagulation or cryotherapy was performed as additional treatment.

Results: The study included 35 tumors in 17 eyes of 14 patients (19 tumors in 8 eyes in the control group and 16 tumors in 9 eyes in the case group). There was 57.22% and 61.73% decrease in tumor thickness in the control and case groups, respectively. This difference was not statistically significant (P=0.12). The decrease in greatest basal tumor dimension in the control group (47.32%) was not significantly different from that in the case group (38.80%). One eye (12.5%) in the control group and 3 eyes (33.3%) in the case group were enucleated.

Conclusion: Adjuvant subtenon carboplatin does not seem to increase the efficacy of systemic chemotherapy in the treatment of intraocular retinoblastoma.

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Introduction

Retinoblastoma is the most common primary intraocular malignancy in children with an incidence of 1 in 15,000 live births.[1] Treatment includes enucleation and external beam radiotherapy (EBRT) for large tumors and cryotherapy, laser therapy and plaque radiotherapy for smaller lesions.[2,3] Therapeutic modalities in retinoblastoma have changed to avoid invasive methods and reduce the rate of enucleation. Chemotherapy and chemoreduction are receiving increasing attention as effective methods for salvage of the eye.[4] Chemotherapy is normally used to shrink small tumors which can subsequently be destroyed using adjuvant treatment such as laser therapy, cryotherapy, thermotherapy, chemothermotherapy, and plaque radiotherapy. The drugs most commonly used

for chemotherapy and chemoreduction are vincristine, etopozide, carboplatin and cyclophosphamide.[3-6]

Considering the side effects of systemic chemotherapy, intravitreal and periocular injections of cytotoxic drugs have received special attention.[5,6] Experimental studies in primates have shown tolerability to periocular carboplatin injections. Another study has reported tumor growth inhibition with multiple subconjuctival carboplatin injections BLHSV-40 transgenic mice.[7] The short-term efficacy of periocular carboplatin has been reported in one case of human retinoblastoma.[8] The purpose of the present study was to determine the effectiveness of adjuvant subtenon carboplatin in patients with intraocular retinoblastoma receiving systemic chemotherapy.

Methods

This double-masked matched randomized clinical trial was conducted on patients referred to Farabi Eye Hospital, Tehran, Iran from 2000 to 2002. Retinoblastoma was diagnosed by a typical tumor appearance on funduscopy (endophytic or exophytic) associated with signs of calcification on orbital CT-scan. Prior to enrollment and randomization, informed consent was obtained from patients' parents.

All patients underwent examination under anesthesia. The anterior segment was examined with a surgical microscope, followed by tonometry using the Schiotz tonometer. Maximum basal tumor dimension was estimated in disc diameter by indirect ophthalmoscopy. B-scan echography was performed with the Nidek-US2500, and maximum tumor thickness was recorded. However, A-scan echography under anesthesia was not feasible. Brain and orbital CT-scan was also performed for all patients. Other findings such as serous retinal detachment, subretinal seeding or presence of subretinal fluid were also recorded.

Patients with gross anterior segment involvement, presence of tumor cells in the anterior chamber, evidence of iris neovasculation, intraocular pressure over 21mmHg, hypopyon, proptosis, or any sign of tumor invasion and spread outside the globe on CT-scan were excluded from the study. The stage of the tumor was categorized using Reese-Ellsworth grouping (1a, 1b, 2a, 2b, 3a, 3b, 4a, 4b, 5a, 5b) and then patients were randomly assigned to receive systemic chemotherapy with subtenon carboplatin injection or systemic chemotherapy alone.

In the present study we administered subtenon carboplatin injection as described by Abramson et al. For this purpose 20mg/2ml of carboplatin (Ebewe, Austria) was injected into the subtenon space in the inferotemporal quadrant with a #27 needle. Topical antibiotics and steroids were prescribed for 1 week. All patients were referred to a pediatric oncologist for further investigation and systemic chemotherapy. This assessment included clinical examination, blood biochemistry, urinanalysis, hepatic tests, bone marrow aspiration and CSF (cerebrospinal fluid) to determine possible metastasis. If metastasis was ruled out, the patient received one of two treatment protocols, VEC (vincristine, etoposide, carboplatin, table 1) or OPEC (oncovine, cyclophosphamide, etoposide, cisplatin, table 2). VEC was prescribed in patients with unilateral involvements and OPEC in bilateral cases. However, in some cases the oncologist changed the systemic chemotherapy program according to blood cell count results.

Table 1. VEC therapeutic regimen

VEC/ Day	Vincristine 0.05 mg/kg	Etoposide 5 mg/kg	Carboplatin 18.6mg/kg
0	+	+	+
1	-	+	+

Table 2. OPEC therapeutic regimen

OPEC/Day	Oncovine 1.05 mg/m²	Cyclophosphamide 600 mg/m²	Etoposide 150 mg/m²	Cisplatin 60 mg/m²
0	+	-	-	+
1	-	-	+	-
4	-	+	-	-

Periodic examinations under anesthesia were performed every 6-8 weeks and included B scan ultrasonography to record maximum tumor thickness, indirect ophthalmoscopy to document maximum basal dimension and thickness based on disc diameter (DD) and repeat carboplatin injection for the case group. The trial regimen included at least 4 carboplatin injections and 6 sessions of VEC or 8 sessions of OPEC chemotherapy. Response to treatment was defined as complete, with total regression of tumor and partial when some of the active tumor mass remained.

Recurrence was defined when active tumor mass reappeared in a tumor that had previously shown partial or complete response.

In each group, possible side effects of the drug regimen were recorded. If the tumor was still active after injections, chemotherapy was continued. After reduction of tumor volume, laser therapy and cryotherapy were employed. The eye was enucleated if the tumor progressed despite treatment.

Confluent photocoagulation was applied in 3 rows around and on the surface of the tumor as much as possible with chalky white intensity. Follow-up examinations were performed by a retina specialist unaware of the patients' treatment protocol.

The effect of treatment in each group was analysed using paired T-test and T-test was used to compare treatment effect between the two groups. Differences between frequencies of variants in groups were analysed using Fisher's exact test or Mann-Whitney test.

Results

Overall 35 tumors in 17 eyes of 13 patients were enrolled in this study.

A) Systemic chemotherapy

This group included 19 tumors in 8 eyes of 8 patients 7-30 months of age (mean 15.3±8.9) consisting of 4 male and 4 female subjects. No positive family history was found in any case and the tumor was unilateral in one case and unifocal in 2 eyes. Two eyes were in stage 5b, 2 eyes were in stage 4 (one 4a the other 4b), 3 eyes were in stage 3 (one 3a the other two 3b) and 1 eye was in stage 2a. Clinical characteristics are shown in table 3.

There were 6-16 chemotherapeutic cycles (mean 8.1±2.03). VEC program was initiated in 5 patients and after 6 sessions, one patient was shifted to OPEC. The OPEC program was initiated in 3 patients, after 10 sessions one patient was shifted to VEC.

Mean initial tumor thickness was 5.57±2.54 mm, which was eventually reduced to 2.36±1.20 mm, indicating a reduction of 57.2±12.8% ($p<0.001$). Mean maximum basal tumor dimension at initiation of treatment was 8.71±6.16 disc diameter, which was reduced to 4.03±3.03 disc diameter, indicating a reduction of 47.3±19.6% ($p=0.026$).

Mean follow-up was 12.5±2 months (range 10-15 months). During follow-up laser photocoagulation was performed in 3 eyes and cryotherapy in1 eye. At the end of treatment, three eyes (%37.5) showed complete regression, 3 eyes had partial regression, one eye (%12.5) demonstrated tumor recurrence and one eye (%12.5) was enucleated (table 4). No significant complications were observed in this group.

Table 3. Clinical features of eyes in the control group

Eye	Age (months)	Tumor stage	Growth pattern	Tumor foci	No of Tumors	SRD	SRS
1	7	IVb	E	multiple	5	-	+
2	10	IIIa	E	multiple	2	+	-
3	7	IIa	E	multiple	3	-	-
4	20	IVb	E	multiple	3	+	-
5	7	IIIb	I	multiple	2	-	+
6	24	IIIb	E	single	1	-	-
7	18	IIIb	E	single	1	-	-
8	30	Vb	I	multiple	2	-	-

SRD: subretinal seeding; SRS: serous retinal detachment; E: endophytic; I: infiltrative

Table 4. Therapeutic regimen and final response in the control group.

Eye	Chemotherapy sessions	Laser	Cryotherapy	Follow-up	Response
1	VEC (7)	-	-	10	complete
2	VEC (6) OPEC (10)	+	-	15	recurrence
3	OPEC(8)	+	-	15	partial
4	VEC (6) OPEC (10)	-	+	14	complete
5	OPEC(8)	-	-	10	partial
6	VEC (6)	+	-	12	partial
7	VEC (11)	-	-	12	complete
8	VEC (10)	-	-	12	enucleated

VEC: vincristine, etoposide, carboplatin; OPEC: oncovine, cyclophosphamide, etoposide, cisplatin

B) Systemic chemotherapy plus subtenon carboplatin

This group included 16 tumors in 9 eyes of 5 patients, consisting of 4 male and 1 female subjects with mean age of 19.1±17.2 months (range 7-48 months). Family history was positive in one case.

The tumor was unilateral in 5 eyes. Five eyes had stage 5b disease, 2 eyes were in stage 3 (one 3a and one 3b) and 2 eyes were in stage 2b. Clinical characteristics are shown in table 5.

There were 6-16 chemotherapeutic cycles (mean, 9.6±4.1). In one case (No.4) after 10 OPEC cycles, treatment was changed to VEC. Eyes in this group received a mean of 7.6±3.1 subtenon carboplatin injections (range 5-15 injections). Mean follow-up was 14.5±5.05 (range 10-27) months (table 6).

Mean initial tumor thickness was 9.01±3.43 mm which was reduced to 3.68±4.14 mm showing a 61.7±29.8% reduction (p=0.004). Maximum basal tumor dimension was 9.38±2.95 disc diameter before treatment and was reduced to 5.36±2.99 disc diameter after treatment indicating a 38.8±28.9% reduction (p=0.004).

Two eyes received laser therapy and one eye received cryotherapy. Eventually, 3 eyes (%33.3) were enucleated all of which were in stage 5b and one eye showed a diffuse growth pattern. Three eyes demonstrated complete regression and 3 eyes showed partial regression. Conjunctival

thickening and globe motility limitation were observed in 4 eyes which received at least 6 injections; one of the 4 eyes that received 7 injections, developed mild periorbital lipid atrophy.

Table 5. Clinical features of eyes in the case group

Eye	Age (months)	Tumor stage	Growth pattern	Tumor foci	Tumors	SRD	SRS
1	48	Vb	E	single	1	+	-
2	24	Vb	E	single	1	-	-
3	7	IIIb	E	single	2	+	-
4	10	Vb	E	multiple	3	-	-
5	12	IIb	E	single	1	-	-
6	48	Vb	E	single	3	+	-
7	7	IIIa	E	single	1	-	-
8	9	IIb	E	single	1	-	-
9	7	Vb	I	multiple	3	-	-

SRD: serous retinal detachment; SRS: subretinal seeding: E: endophytic; I: infiltrative

Table 6. Therapeutic regimen and final response in the case group

Eye	injections	Chemotherapy sessions	Laser	Cryotherapy	Follow-up	response
1	10	VEC (14)	-	-	14	enucleated
2	15	VEC (6)	+	-	27	complete
3	6	VEC (6)	-	-	10	complete
4	8	OPEC(10) VEC (6)	-	-	15	enucleated
5	5	VEC (6)	+	-	12	partial
6	7	VEC (8)	-	-	14	partial
7	6	VEC (15)	-	+	15	partial
8	6	OPEC (8)	-	-	14	complete
9	6	VEC (6)	-	-	10	enucleated

VEC: vincristine, etoposide, carboplatin; OPEC: oncovine, cyclophosphamide, etoposide, cisplatin

C) Comparison of two treatment protocols

The study groups had comparable age and sex characteristics (P=0.10). Bilateral involvement was present in 7 (%87.5) and 4 (%44.4) patients in controls and cases respectively (p=0.131 Fisher's exact test). Disease stage was also comparable in the two groups (p=0.1 Mann-Whitney test). The groups were similar in terms of serous retinal detachment, subretinal seeding, type and number of systemic chemotherapy sessions. Follow-up duration was also similar (p=0.20).

Initial tumor thickness, was significantly less in the control group (p=0.035). However maximum basal diameter was not significantly different in the two groups. After treatment no significant difference was observed in the two groups in terms of reduction in tumor thickness and maximal tumor basal diameter (Tables 7&8).

Table 7. Tumor thickness on echography before and after treatment

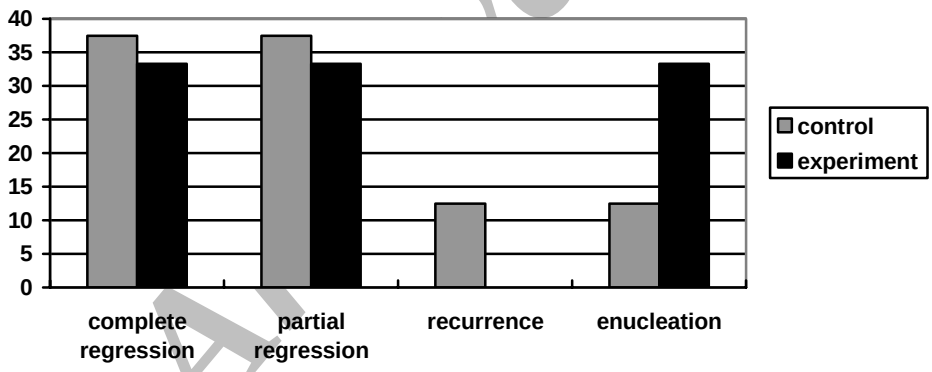
	Tumor thickness			
Groups	Pre-treatment	Post-treatment	Reduction (%)	P value
Control (n=8)	5.5±2.5	2.3±1.2	57.2±12.8	0.001
Case (n=9)	9.0±3.4	3.6±4.1	61.7±29.8	0.004
P Value	0.035	0.40	0.69	

Table 8. Basal tumor dimension on funduscopy before and after treatment

	Basal tumor dimension (disc diameter)			
Groups	Pre-treatment	Post-treatment	Reduction (%)	P value
Control (n=8)	8.7±6.1	4.0±3.0	47.3±19.6	0.026
Case (n=9)	9.3±2.9	5.3±2.9	38.8±28.9	0.004
P Value	0.77	0.37	0.49	

The final outcome of the treated eyes in the two groups did not show any significant difference: rate of complete resgression was 37.5% in the control group and 33.3% in the case group. Partial regression was observed in 37.5% and 33.3% of patients in the control and case groups respectively. Enucleation was performed in 12.5% and 33.3% of controls and cases respectively. Tumor recurrence occurred in 12.5% in the control group and none of the eyes in the case group (figure -1).

Figure 1: Treatment response in study groups



Discussion

Our results indicated that adjuvant subtenon carboplatin injection was not superior to systemic chemotherapy alone in eyes with intraocular retinoblastoma in terms of reduction in tumor size. In the control group 3 eyes (%37.5) had complete regression and 3 eyes had partial regression, similarly in the case group 3 eyes (%33.3) had complete regression and 3 eyes had partial regression. One of 8 eyes (12.5%) in the control group and 3 of 9 eyes (%33.3) in the case group were enucleated. Enucleation was performed in 50% and 60% of eyes in stage 5 disease in the control and case groups respectively. No significant side effects or optic nerve atrophy were observed, however 4 eyes that received 6 or more injections had some degree of conjunctival thickness or fibrosis.

A previous previous animal study indicated that repeated injections of subconjuctival carboplatin in transgenic mouse with retinoblastoma inhibited tumor growth in 50% of the eyes. [9]
In a non-comparitive study, Abramson and colleagues, treated 13 eyes of 11 patients with subconjuctival carboplatin; mean number of injections for each eye was 3 times and mean injection interval was 21 days. However some patients had received different treatments previously, such as plaque radiotherapy and systemic chemotherapy. Three out of 5 eyes with vitreous involvement and 2 of 5 eyes with retinal tumors demonstrated favorable response. One case of optic atrophy was observed, this patient was also receiving other focal treatment (photocoagulation and cryotherapy), which was considered the cause of optic nerve atrophy. One case of periorbital fat atrophy was reported in an eye which received seven injections.[10]

In our previous study on intravitreal carboplatin injection, the globe was salvaged in 75% of patients receiving systemic chemotherapy alone and in 91% of patients receiving chemotherapy plus intravitreal carboplatin.[11] However, these eyes were in lower stages of involvement than in the current report, and the duration of follow up was shorter.

Shield reported 52 eyes managed with chemoreduction with 6 cycles of VEC with or without secondary treatment. After one year, 22% of the eyes required enucleation or EBRT but there was no need for enucleation in the group which received secondary treatment.[12] In another study on 158 eyes managed with 6 sessions of chemoreduction with VEC plus local treatment, Shield reported that 53% of eyes in stage 5 were enucleated after 28 months of follow-up[13], which is comparable to our study.

Gallie and colleagues reported that 88% of stage 5b cases stayed clear of recurrence within a short follow up period of 4 months, which shows a better response to treatment than our series.[6] However, our study had a longer duration of follow up (14 months for the treatment group and 12 months for the control group).

Gunduz and Shield in their study on 11 eyes in stage 5 stated that after 6 cycles of chemoreduction with VEC and focal treatment, 25% required EBRT or enucleation after 28 months of follow up.[14] In a similar study Freidman reported a 23% need for EBRT or enucleation.[15]

Our study was designed as a randomized matched clinical trial, which is considered one of its advantages. There were limitations to this study that should be considered, such as employment of two different systemic chemotherapy regimens, the small number of patients and lack of A-scan ultrasonography during examination under general anesthesia. In addition there was a chance that the examiner could guess the treatment group of eyes which had received multiple injections by their appearance.

In conclusion although systemic chemotherapy alone was effective in reducing tumor size and salvage of the globe, adjuvant subtenon carboplatin injection did not increase the efficacy of such treatment.

References

1. Finger PT, Czechonska G, Demivel H, Rausen A. Chemotherapy for retinoblastoma: a current topic. Drugs 1999; 58:983-996.
2. Shields JA, De Potter P. New treatment modalities for retinoblastoma. Curr Opin Ophthalmol 1990; 7:20-26.
3. Roatry JD, Mc Lean IW, Zimmermann LE. Incidence of second neoplasms in patients with bilateral retinoblastoma. Ophthalmology 1988; 95:1983-1987.
4. Shields CL, Shields JA, Needle M. Combined chemoreduction and adjuvant treatment for intraocular retinoblastoma. Ophthalmology 1997; 104:2101-2111.
5. Gunalp I, Gunduz K, Arslan-Y. Retinoblastoma in Turkey: treatment and prognosis. Jpn J Ophthalmol 1996; 40:95-102 (Abstract).
6. Gallie BL, Budning A, Deboer G, et al. Chemotherapy with focal therapy can cure intraocular retinoblastoma without radiotherapy. Arch Ophthalmol 1996; 114:1321-1328.

7. Mendelson ME, Abramson DH, Madden T, et al. Intraocular concentration of chemotherapeutic agents after systemic or local administration. Arch Ophthalmol 1998; 116:1209-1212.
8. Draper GI, Sanders BM, Kingstone JE. Second primary neoplasm in patients with retinoblastoma. Br J Cancer 1986; 53:661-671.
9. Murray TG, Cicciarelli N, O'Brien JM, et al. Subconjunctival carboplatin therapy in the treatment of transgenic murine retinoblastoma. Arch Ophthalmol 1997; 115:1286-1290.
10. bramson DH, Frank CM, Dunkel IJ. A phase I/II study of subconjunctival carboplatin for intraocular retinoblastoma. Ophthalmology 1999; 106:1947-1950.
11. Karkhaneh R, Moradi-Moghadam M, Chams H, Vosoogh P, Valaie N. Intravitreal carboplatin for treatment of intraocular retinoblastoma. Bina J Ophthalmol 2000; 2:95-105.
12. Shields CL, De Potter P. Chemoreduction in the initial management of intraocular retinoblastoma. Arch Ophthalmol 1996; 114:1330-1338.
13. Shields CL, Honavar GS, Meadows TA, et al. Chemoreduction plus focal therapy for retinoblastoma: factors predictive of need for treatment with external beam radiotherapy or enucleation. Am J Ophthalmol 2002; 133:657-664.
14. Gunduz K, Shields CL, Shields JA, et al. The outcome of chemoreduction treatment in patients with Reese-Ellseworth group V retinoblastoma. Arch Ophthalmol 1998; 116:1613-1617.
15. Friedman DL, Himelstein B, Shield CL. Chemoreduction and local ophthalmic therapy for intraocular retinoblastoma. J Clin Oncol 2000; 18:2-17.