Management and Outcome of Retinoblastoma with Vitreous Seeds

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Purpose: To report the treatment response of retinoblastoma with vitreous seeds to high-dose chemotherapy coupled with periocular carboplatin.

Design: Retrospective, interventional case series.

Participants: Consecutive patients with retinoblastoma with vitreous seeds managed over 10 years at a comprehensive ocular oncology center and followed up for at least 12 months after the completion of treatment were included in this study. Institutional review board approval was obtained.

Intervention: High-dose chemotherapy with a combination of vincristine, etoposide, and carboplatin in patients with focal vitreous seeds and additional concurrent periocular carboplatin in patients with diffuse vitreous seeds.

Main Outcome Measures: Tumor regression, vitreous seed regression, and eye salvage.

Results: After excluding the better eye of bilateral cases, 101 eyes of 101 patients were part of the final analysis. All the patients belonged to Reese-Ellsworth group VB, but on the International Classification of Retinoblastoma (ICRB), 21 were group C, 40 were group D, and 40 were group E. The mean basal diameter of the largest tumor was 11.8±4.7 mm. Mean tumor thickness was 7.5±4.0 mm. Vitreous seeds were focal in 21 eyes and diffuse in 80 eyes. Chemotherapy cycles ranged from 6 to 12 (median, 6). Seventy-three eyes with diffuse vitreous seeds received a 15-mg posterior sub-Tenon carboplatin injection (range, 1−13 mg; median, 6 mg). Follow-up duration ranged from 13.4 to 129.2 months (median, 48 months). External beam radiotherapy (EBRT) was necessary in 33 eyes with residual tumor, vitreous seeds, or both. In all, 20 eyes (95%) with ICRB group C retinoblastoma, 34 eyes (85%) with group D retinoblastoma, and 23 eyes (57.5%) with group E retinoblastoma were salvaged. Of 77 eyes that were salvaged, 74 (96%) had visual acuity of 20/200 or better. Twenty-four of 33 chemotherapy failures (73%) regressed with EBRT. None of the patients demonstrated second malignant neoplasm or systemic metastasis. Factors predicting tumor regression and eye salvage were bilateral retinoblastoma and absence of subretinal fluid. Factors predicting vitreous seed regression were absence of subretinal fluid and subretinal seeds.

Conclusions: Intensive management with primary high-dose chemotherapy and concurrent periocular carboplatin, and EBRT selectively in chemotherapy failures, provides gratifying outcome in retinoblastoma with vitreous seeds. *Ophthalmology 2014;121:517-524 © 2014 by the American Academy of Ophthalmology.*

The management of retinoblastoma has undergone a paradigm change in the recent past. Although the focus continues to be on improved survival and safety of treatment methods, the emphasis is now on eye salvage and optimization of residual vision. A substantial reduction in the frequency of enucleation has been achieved in the last few decades, both for unilateral and bilateral retinoblastoma.[1−4] Similarly, the proportion of patients treated with external beam radiotherapy (EBRT) has decreased sharply from 35% in the late 1980s to approximately 7% now.[5] Concurrently, there has been an increasing interest in the use of alternative eye- and vision-conserving methods of treatment.[2,6−39]

Chemotherapy is the current standard of care for retinoblastoma. Chemotherapy can be delivered systemically, regionally, or locally.[2,6−14,16−36] Standard triple-drug systemic chemotherapy (vincristine+etoposide+carboplatin) is most effective in tumors without associated subretinal fluid, subretinal seeds, or vitreous seeds.[2,6−14,35] Chemotherapy provides satisfactory tumor control for Reese-Ellsworth groups I through IV, with treatment failure necessitating additional external beam radiotherapy in only 10% and enucleation in 15%.[11] However, 47% of patients with Reese-Ellsworth group V tumors needed EBRT and 53% required enucleation.[11] In another study, eye salvage was achieved in 47% of International Classification of Retinoblastoma (ICRB) group D eyes overall, and in only 30% in eyes with diffuse vitreous seeds.[35] Cohen et al[13] could salvage only 2 of 18 eyes with Reese-Ellsworth group V retinoblastoma with standard chemotherapy alone. Kingston et al[6] could salvage 8 of 12 eyes (67%) with vitreous seeds with chemotherapy coupled with EBRT. Overall, 30% to 77% of eyes with vitreous seeds that underwent primary chemotherapy ultimately needed enucleation (Table 1).

More recently, the role of superselective chemotherapy is being explored in the management of advanced retinoblastoma.[16−21] There is a 64% probability of eye salvage

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Table 1. Outcome of Retinoblastoma with Vitreous Seeds: A Review of the Literature

Authors	Year	No.	Type of Vitreous Seeds	Management	Use of External Beam Radiotherapy	Enucleation, n (%)	Eye Salvage, n (%)	Vision Salvage, n (%)
Murphree et al[7]	1996	18	Diffuse (n = 18)	CRD	Yes (n = 4)	14 77)	4 (22)	NA
Gallie et al[9]	1996	22	NA	CRD	Yes (n = 3)	11 (50)	11 (50)	8 (36)
Kingston et al[6]	1996	12	NA	CRD	Yes (n = 12)	4 (33)	8 (66)	NA
Shields et al[10]	1997	24	Focal (n = 7), diffuse (n = 17)	CRD	Yes (NA)	8 (33)	16 (67)	NA
Shields et al[2]	2002	11	Focal (n = 6), diffuse (n = 5)	CRD	Yes (n = 4)	7 (64)	4 (36)	NA
Shields et al[12]	2002	54	Focal (n = 32), diffuse (n = 22)	CRD	Yes (n = 4)	16 (30)	38 (70)	NA
Chan et al[14]	2009	5	NA	CRD	Yes (NA)	2 (40)	3 (60)	NA
Mallipatna et al[31]	2011	2	Diffuse	CRD, PO topotecan	No	2 (100)	0 (0)	NA
Shields et al[18]	2011	9	Diffuse	CRD, IAC	Yes (n = 2)	1 (12)	8 (88)	NA
Abramson et al[20]	2012	31	Focal (n = 14), diffuse (n = 14), NA (n = 3)	CRD, IAC	Yes (NA)	8 (25)	23 (75)	NA
Kivelä et al[24]	2012	2	NA	CRD, IV methotrexate	No	1 (50)	1 (50)	NA
Munier et al[25]	2012	23	Diffuse	CRD, IV melphalan	No	3 (17)	20 (83)	NA
Ghassemi and Shields[26]	2012	12	Diffuse	CRD, IV melphalan	No	6 (50)	6 (50)	NA
Manjandavida et al	Current study	101	Focal (n = 21), diffuse (n = 80)	HD CRD, PO carboplatin	Yes	24 (24)	77 (77)	74 (74)

CRD = chemoreduction; HD = high dose; IAC = intra-arterial chemotherapy; IV = intravitreal; NA = not applicable; PO = periocular.

in eyes with vitreous seeds.[20] In another study, 67% of eyes in the subgroup of patients with vitreous seeds underwent enucleation after intra-arterial chemotherapy.[17,18] Local chemotherapy, intraocular or periocular, provides high intravitreal drug concentration and helps manage vitreous seeds.[22–33] However, intravitreal chemotherapy has not yet gained wide acceptance because of the apprehension of possible extraocular dissemination and pending standardization of dose and frequency of administration.[22–27] Periocular chemotherapy also results in high intravitreal drug level, and periocular carboplatin injection has been found to be an option in the management of retinoblastoma with vitreous seeds.[28–33]

Retinoblastoma with vitreous seeds accounts for approximately 30% (280 of 957 eyes) of all patients with retinoblastoma in our clinic,[40] and the situation is much worse in low-income countries.[37] Clearly, there is a need to improve eye salvage in patients with retinoblastoma with vitreous seeds using cost-effective treatment protocols but without compromising patient safety and survival. Our study involves a large series of such patients and focuses on the role of primary high-dose chemotherapy and periocular carboplatin.

Methods

Our retrospective, noncomparative, interventional case series included 137 eyes of 101 consecutive patients with retinoblastoma with vitreous seeds managed with high-dose chemotherapy with or without periocular carboplatin from July 2000 through December 2010 and who had completed at least 12 months of follow-up after the last treatment. After excluding the better eye of patients with bilateral vitreous seeds, 101 eyes of 101 patients were analyzed. Our objective was to study tumor regression, vitreous seed regression, and eye salvage after high-dose chemotherapy alone in eyes with focal vitreous seeds and high-dose chemotherapy and periocular carboplatin in eyes with diffuse vitreous seeds. The study setting was a multispecialty retinoblastoma treatment facility at a tertiary care eye hospital in southern India. Institutional review board approval was obtained.

The data were collected prospectively and were analyzed retrospectively. The demographic information, clinical findings, treatments, and visual outcomes were tabulated. Demographic data recorded at the initial visit included patient age at diagnosis (in months), gender (male or female), hereditary pattern (familial or sporadic), laterality (unilateral or bilateral), and the involved eye (right, left, or both). The total number of tumors per eye and grouping by the Reese-Ellsworth classification and ICRB[35] were recorded. Each tumor was evaluated for the greatest basal dimension (in millimeters) and the proximity of the nearest tumor margin to the optic disc and foveola using indirect ophthalmoscopy. Tumor height (in millimeters) was assessed by B-scan ultrasonography and, where that was not possible, was estimated clinically. The presence and extent of subretinal fluid (localized, diffuse, and clock hours) and of tumor seeding in the vitreous (focal, diffuse) and subretinal space (focal, diffuse) were assessed. Vitreous seeds and subretinal seeds were defined as focal if located 3 mm or less from the tumor and as diffuse if located more than 3 mm from the tumor.

The chemotherapy protocol included a combination of high-dose intravenous vincristine, etoposide, and carboplatin (Table 2) in all the patients with vitreous seeds. Every child received a minimum of 6 cycles of high-dose chemotherapy. Chemotherapy was extended up to a maximum of 12 cycles if there were residual tumors or vitreous seeds beyond 6 cycles, vision salvage was possible (determined based on the tumor location), and enucleation (only eye with visual potential) or EBRT (heritable retinoblastoma with age $\leq$12 months) were not feasible. Periocular carboplatin was administered specifically in patients with diffuse vitreous seeds that remained diffuse and viable as judged clinically after the initial 2 cycles of high-dose chemotherapy. It was