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Postenucleation adjuvant chemotherapy with vincristine, etoposide, and carboplatin for the treatment of high-risk retinoblastoma.

Swathi Kaliki
Wills Eye Institute

Carol L Shields
Wills Eye Institute

Sanket U Shah
Wills Eye Institute

Ralph C Eagle
Wills Eye Institute

Jerry A Shields
Wills Eye Institute

See next page for additional authors

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Swathi Kaliki, M.D.

Carol L. Shields, M.D.

Sanket U. Shah, M.D.

Ralph C. Eagle, Jr, M.D.

Jerry A. Shields, M.D.

Ann Leahey, M.D.

From the Ocular Oncology Service (SK, CLS, SUS, JAS), and the Ophthalmic Pathology Department (RCE), Wills Eye Institute, Thomas Jefferson University, Philadelphia, PA, and the Children's Hospital of Philadelphia, Philadelphia, PA (AL).

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Inquiries to Carol L. Shields, M.D., Ocular Oncology Service, Suite 1440, Wills Eye Institute, 840 Walnut Street, Philadelphia, PA 19107. Email carol.shields@shieldsoncology.com

Key words:

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Précis

Analysis of 52 eyes with high-risk retinoblastoma managed with post-enucleation adjuvant chemotherapy using vincristine sulfate, etoposide phosphate, and carboplatin showed no evidence of systemic metastasis in any case over a mean follow-up of 66 (12 to 202) months.

Abstract

Purpose: To determine the efficacy of post-enucleation adjuvant chemotherapy with vincristine sulfate, etoposide phosphate and carboplatin (VEC) in the prevention of metastasis for patients with high-risk retinoblastoma.

Methods: Retrospective, nonrandomized, interventional case series of 52 eyes in 51 patients with high-risk retinoblastoma consisting of tumor invasion into the anterior segment, posterior uvea 3 mm or greater, post-laminar optic nerve, or any combination of posterior uvea and optic nerve involvement.

Results: Of 51 consecutive patients with high-risk retinoblastoma, there were 30 males (59%) and 21 females (41%), with a median age of 28 months at diagnosis. All 52 eyes were classified as group E. The main histopathologic risk factors included anterior segment invasion (7 [13%]), isolated massive posterior uveal invasion of 3mm or greater (6 [12%]), isolated postlaminar optic nerve invasion (15 [29%]), or any posterior uveal invasion with any optic nerve involvement (24 [46%]). There was additional invasion into the sclera (3 [6%]) and extrascleral structures including the orbit (1 [2%]). A single histopathologic high-risk factor was present in 32 eyes (62%), whereas 20 eyes (38%) manifested 2 or more high-risk characteristics. Based on previously published series, untreated high-risk retinoblastoma carries at least a 24% risk for metastatic disease. In the present series, using vincristine sulfate, etoposide phosphate, and carboplatin in all cases, there was no metastasis during a mean follow-up of 66 months (median [range], 55 [12-202] months).

Conclusion: Retinoblastoma with invasion into the postlaminar optic nerve and/or posterior uvea is at high risk for metastasis and death. In this study, post-enucleation chemotherapy using vincristine sulfate, etoposide phosphate, and carboplatin was effective in preventing metastasis in every case (100%).

Retinoblastoma (RB) is the most common primary malignant intraocular tumor in the world, and the second most common primary intraocular malignancy in the Western Hemisphere, after uveal melanoma. It is estimated that 7202 to 8102 new cases of RB are diagnosed worldwide each year.[1] The mean age-adjusted incidence of RB in children aged birth to 4 years is 11.8 per million, with a 5-year survival of 96.5% in the United States of America.[2,3] On the basis of the mortality data and birth rates in corresponding continents, it is estimated that 3001 to 3376 children die of RB annually, most deaths occurring in less developed areas, such as parts of Africa (death rate of 70%) and Asia (death rate of 42%).[1] Poor survival in these regions is due to late diagnosis, leading to advanced malignant neoplasms showing invasive features that are prone to micrometastatic disease.[1,4,5]

In RB, there are histopathologic factors that have been identified from enucleated eyes predictive of the development of metastatic disease and related mortality.[6-9] Patients demonstrating such risk factors are often given postenucleation adjuvant chemotherapy for protection from metastasis and improvement in survival.[10]

There is some controversy regarding the exact definition of high-risk histopathologic features[11,12] and further debate regarding the most effective chemotherapeutic protocol for treatment of such patients.[13,14] In this retrospective, noncomparative study, we investigated the role of a single chemotherapeutic protocol using vincristine sulfate, etoposide phosphate, and carboplatin in the prevention of RB metastasis in high-risk cases following enucleation.

Methods

This study was a retrospective, non-randomized, non-comparative, interventional case series. Institutional review board approval was obtained. The medical records of all patients with RB managed with enucleation on the Ocular Oncology Service at Wills Eye Institute in Philadelphia from January 1, 1994, through December 31, 2010, were reviewed. The histopathologic features of the enucleated specimen were reviewed. High-risk histopathologic features were defined as the presence of 1 or more of the following features: tumor invasion into the anterior segment, posterior uvea of 3 mm or greater,

postlaminar optic nerve involvement, or any posterior uveal invasion with any optic nerve involvement. (Figure 1). Optic nerve invasion was classified as prelaminar, at the lamina cribrosa, postlaminar, and/or to the site of transection. Additional invasion into the sclera and extrascleral structures including the orbit were recorded. Patients with high-risk RB who received post-enucleation adjuvant chemotherapy with vincristine sulfate, etoposide phosphate and carboplatin (VEC), and with a minimum follow-up of 1 year were included in this study. High-risk RB patients treated with chemotherapeutic agents other than VEC, and patients enrolled in Children's Oncology Group study ARET-0332, were excluded.

The medical records were reviewed for clinical and histopathologic findings. The demographic data included age at diagnosis (months), sex and race. Genetic results (germline, somatic) for RB were recorded when available. The hereditary pattern (sporadic, familial) and prior local or systemic treatment for RB was noted. The presenting symptoms, duration of symptoms (days) and visual acuity were recorded. The tumor laterality (unilateral, bilateral), total number of tumors per eye, International Classification of Retinoblastoma, Reese-Ellsworth classification, intraocular pressure (millimeters of mercury Hg by Schiotz tonometry), and status of the anterior chamber, iris, ciliary body, optic nerve, choroid, and vitreous were noted. Each tumor was measured for greatest basal dimension (millimeters), thickness (millimeters), and proximity to the optic disc and foveola (millimeters). Clinical features of anterior chamber seeding, hyphema, iris neovascularization, vitreous seeding, vitreous hemorrhage, subretinal seeding, tumor calcification, retinal detachment, neovascularization of the optic disc, neovascularization elsewhere, optic disc edema, and choroidal invasion were noted. All findings were documented by large fundus drawings, fundus photography with RetCam camera (Massie Industries, Dublin, California), fluorescein angiography, and ultrasonography.

The initial treatment and reason for enucleation were recorded. The eyes were sent for histopathologic assessment, and the findings were reviewed for high-risk features. Other histopathologic findings noted were growth pattern (exophytic, endophytic, combined exophytic-endophytic), tumor location (quadrant), presence of necrosis and dystrophic calcification, depth and lateral extent of choroidal invasion (millimeters), depth of postlaminar optic nerve invasion (millimeters) and tumor differentiation.

In patients with high-risk RB, post-enucleation adjuvant therapy by intravenous VEC was administered. Dosage (Table 1), number of cycles, and complications of VEC systemic chemotherapy were recorded. After VEC chemotherapy, metastatic evaluation included history and physical examination, computed tomography and/or magnetic resonance imaging of the orbit and brain repeated at 6-month intervals until age 5 years. Systemic findings from the metastatic evaluation, duration of follow-up (months) and the final systemic outcome (alive without metastasis, alive with metastasis, alive with second malignant neoplasm, dead from metastasis, dead from second malignant neoplasm, or dead from other causes) were recorded.

Results

Of 406 eyes enucleated for RB during this period, 66 eyes (16.3%) had 1 or more high-risk histopathologic features predictive of systemic metastasis. Of these 66 eyes, 52 eyes (79%) of 51 patients were treated with VEC with a minimum follow-up of 1 year and were included in this study. The demographic data are listed in Table 2.

The clinical features at presentation are listed in Table 3. Five (10%) patients had a history of previous intraocular surgery, which included vitrectomy and sclera buckle (n=2), vitrectomy alone (n=2) and anterior chamber tap (n=1).

The classification of each eye using Reese Ellsworth classification revealed 51 group Vb (98%) and 1 group Va (2%). According to the International Classification of Retinoblastoma, all 52 eyes (100%) were group E.

Enucleation was preceded by systemic chemotherapy in 4 patients (8%), external beam radiotherapy in 1 (2%), plaque radiotherapy in 1 (2%), and subconjunctival carboplatin in 1 (2%). The reason for enucleation included massive tumor involving 50% or more of the vitreous with no visual potential in 45 eyes (87%), recurrence after chemoreduction in 4 (8%), recurrence after external beam radiotherapy in 1 (2%), recurrence after plaque in 1 (2%), and necrotic tumor with orbital inflammation in 1 (2%).

The histopathologic features are listed in Table 4. All cases with scleral and/or extrascleral invasion also had additional postlaminar and/or massive choroidal invasion. High-risk features were noted in the right eye in 24 patients (47%), left eye in 26 (51%) and both eyes in 1 (2%). The optic nerve stump at enucleation was a mean length of 15 mm (median, 14 mm; range, 8-22 mm).

All 51 patients received intravenous chemotherapy using VEC standard dose (Table 1). The mean number of VEC cycles per patient was 6 (median [range] 6 [4-6]). There were 4 patients (8%) who received 4 cycles of VEC, and the remaining patients received 6 cycles of VEC. The only chemotherapy-related complication was pneumonia in 1 (2%). There was no case of etoposide-related leukemia. One patient (2%) had extrascleral extension along with the high-risk feature of combined optic nerve and choroidal invasion, for which chemotherapy and additional orbital external beam radiotherapy was given after enucleation.

All patients (100%) were followed for more than 1 year and the mean duration of follow-up after adjuvant chemotherapy was 66 months (median [range], 55 [12-202] months). Of 51 patients, 43 (84%) had more than 2 years' follow-up, 41 (80%) had more than 3 years' follow-up, and 22 (43%) patients had more than 5 years' follow-up. The incidence (95% confidence interval) of metastasis was 0% [0 to 6%) at 1 year, 0% (0 to 7%) at 3 years, and 0% (0 to 14%) at 5 years. There was no second malignant neoplasm or death in any case.

Discussion

In nations with advanced medical care, the incidence of metastasis in children with RB is less than 10%.[15] The risk for metastasis greatly increases with histopathologic evidence of high-risk features. In a study from our institution, Honavar and associates[10] found that untreated patients with high-risk histopathologic features developed metastases in 24% of cases, often leading to death. This risk could be much greater in undeveloped nations where high-risk features are more extreme, with macroscopic rather than microscopic invasion. The use of postenucleation adjuvant chemotherapy has been recommended for patients with high-risk features on histopathologic analysis to eradicate presumed micrometastases before they are clinically manifest and to reduce ultimate death.[10,13]

There is considerable controversy in the definition of risk factors for RB metastasis based on histopathologic features. There is also debate regarding the most effective treatment strategies for

affected patients. In previous studies, histopathologic risk factors for RB metastasis included anterior segment invasion, massive uveal invasion (defined as ≥2 mm), scleral infiltration, extrascleral invasion, postlaminar optic nerve invasion, and invasion to the site of surgical transection of the optic nerve.[12,16,17] Following enucleation, the incidence of high-risk histopathologic features has varied from 7% to 9% for anterior segment invasion,[8,17] 12% to 42% for choroidal invasion,[5,7-9,17] 8% to 12% for scleral invasion,[5,8,9,17] 2% to 20% for extrascleral invasion,[5,8,9,17] 6% to 28% for invasion of postlaminar optic nerve,[5,6,8,9,17,18] 1% to 38% for involvement of optic nerve to surgical transection.[5,6,7,8,9,17,18]

In a recent comprehensive report on histopathologic findings following enucleation in 297 untreated eyes of RB, Eagle[16] identified high-risk features in 55 eyes (18.5 %). In these 55 eyes, these features included massive (defined as ≥3mm) uveal invasion with no optic nerve invasion (8 [14.5%]), massive uveal invasion with prelaminar optic nerve invasion (7 [12.7%]), massive uveal invasion with postlaminar optic nerve invasion (10 [18.2%]), postlaminar optic nerve invasion with no uveal invasion (18 [32.7%]), postlaminar optic nerve invasion with nonmassive uveal invasion (3 [5.5%]), combined nonmassive uveal invasion without postlaminar optic nerve invasion (2 [3.6%]), and anterior segment involvement (8 [14.5%]).

According to Chantada and associates,[12] there are world disparities in risk definition and management of RB. On the basis of our previous experience, we believe that anterior segment invasion, massive posterior uveal invasion of 3 mm or greater, postlaminar optic nerve invasion, or a combination of any degree of posterior uveal and optic nerve invasion pose a risk; therefore, we include these 4 factors in our definition as high-risk. The significance of isolated anterior segment involvement remains debatable, but we have previously witnessed metastasis in such cases, so this was included as a factor.[10] Some authors[5,13] have suggested that anterior segment involvement and isolated choroidal invasion are not risk factors for metastasis. The other major source of variation is related to the definition of massive choroidal invasion.[12] In a survey by the International Retinoblastoma Staging Working Group, composed of 58 members from 24 countries in 4 continents, at least 5 different criteria have been reported including full-thickness choroidal invasion with at least 1 cell adherent to the sclera, full invasion greater than 50% thickness of the choroid or more than 1 cluster, deep invasion greater than 50% of the thickness of the choroid, diffuse choroidal invasion of more than 3 clusters, and invasion greater than 3 mm in largest dimension or tumor noted on gross examination. For consensus in

that group, the criterion for massive choroidal invasion was agreed to be maximum diameter (thickness or width) of tumor at 3 mm or greater.[12]

A search for the most effective chemotherapy for RB has been underway since the 1950s.[19-22] Previous studies on adjuvant chemotherapy for high-risk RB have revealed several protocols including agents such as vincristine sulfate, doxorubicin hydrochloride, cyclophosphamide, etoposide, cisplatin, carboplatin, and cyclosporine.[14,23] As shown in Table 5, postenucleation adjuvant chemotherapy regimens have varied over the years. The metastatic rate has ranged from 4% in a study of 26 cases in which vincristine sulfate and cyclophosphamide was used to 33% in a study of 24 cases in which vincristine sulfate, cyclophosphamide, and doxorubicin was used.[26,27] Mustafa and associates[30] studied the effect of vincristine sulfate, doxorubicin, and cyclophosphamide in high-risk RB and found distant metastasis and subsequent death in 19% cases. They concluded that alternative chemotherapeutic agents should be considered for patients with such high-risk features. Uusitalo and associates[31] studied 129 patients using variable regimens and concluded that chemoprophylaxis was beneficial in patients with tumor extending beyond the lamina cribrosa. Honavar and colleagues[10] conducted a retrospective, nonrandomized comparative study of 80 patients with high-risk RB, in which 58% of patients received adjuvant therapy and 42% did not receive adjuvant therapy for various reasons. A significant difference was found in the rate of metastasis between the group that had received adjuvant therapy (4%) and the group that had not (24%). The beneficial effect of adjuvant therapy was statistically significant in subgroups with massive choroidal infiltration and/or postlaminar optic nerve invasion.

In our study, we used a standard multi-agent chemotherapeutic protocol of VEC in every case of high-risk RB. With this regimen, there was no case of metastasis or death during the mean follow-up period of more than 5 years. These same chemotherapeutic agents have proven effective as neoadjuvant chemotherapy.[33] On the basis of our results, VEC is impressively effective for postenucleation high-risk RB in the prevention of systemic metastases, thereby improving survival.

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References:

1. Kivela T. The epidemiological challenge of the most frequent eye cancer:retinoblastoma, an issue of birth and death. *Br J Ophthalmol.* 2009;93(9):1129-1131.

2. Broaddus E, Topham A, Singh AD. Incidence of retinoblastoma in the USA:1975-2004. *Br J Ophthalmol.* 2009;93(1):21-23.

3. Broaddus E, Topham A, Singh AD. Survival with retinoblastoma in the USA:1975-2004. *Br J Ophthalmol.* 2009;93(1):24-27.

4. MacKay CJ, Abramson DH, Ellsworth RM. Metastatic patterns of retinoblastoma. *Arch Ophthalmol.* 1984;102(3):391-396.

5. Kopelman JE, McLean IW, Rosenberg SH. Multivariate analysis of risk factors for metastasis in retinoblastoma treated by enucleation. *Ophthalmology.* 1987;94 (4):371-377.

6. Shields CL, Shields JA, Baez K, Cater JR, De Potter P. Optic nerve invasion of retinoblastoma. Metastatic potential and clinical risk factors. *Cancer.* 1994;73(3):692-698.

7. Shields CL, Shields JA, Baez KA, Cater J, De Potter PV. Choroidal invasion of retinoblastoma: metastatic potential and clinical risk factors. *Br J Ophthalmol.* 1993;77(9):544-548.

8. Messmer EP, Heinrich T, Hopping W, de Sutter E, Havers W, Sauerwein W. Risk factors for metastases in patients with retinoblastoma. *Ophthalmology.* 1991;98(2):136-141.

9. Khelfaoui F, Validire P, Auperin A, et al. Histopathologic risk factors in retinoblastoma: a retrospective study of 172 patients treated in a single institution. *Cancer*. 1996;77(6):1206-1213.

10. Honavar SG, Singh AD, Shields CL, Meadows AT, Demirci H, Cater J, Shields JA. Postenucleation adjuvant therapy in high-risk retinoblastoma. *Arch Ophthalmol.* 2002;120(7):923-931.

11. Sastre X, Chantada GL, Doz F, et al. International Retinoblastoma Staging Working Group. Proceedings of the consensus meetings from the International Retinoblastoma Staging Working Group on the pathology guidelines for the examination of enucleated eyes and evaluation of prognostic risk factors in retinoblastoma. *Arch Pathol Lab Med.* 2009;133(8):1199-1202.

12. Chantada GL, Doz F, Orjuela M, et al. International Retinoblastoma Staging Working Group. World disparities in risk definition and management of retinoblastoma: a report from the International Retinoblastoma Staging Working Group. *Pediatr Blood Cancer.* 2008;50(3):692-694.

13. Chantada GL, Dunkel IJ, de Davila MT, Abramson DH. Retinoblastoma patients with high risk ocular pathological features: who needs adjuvant therapy? *Br J Ophthalmol*. 2004;88(8):1069-1073.

14. Makimoto A. Results of treatment of retinoblastoma that has infiltrated the optic nerve, is recurrent, or has metastasized outside the eyeball. *Int J Clin Oncol*. 2004;9(1):7-12.

15. Young JJL, Smith MA, Roffers SD, et al. In: Ries LAG, Smith MA, Gurney JG, et al. Cancer

incidence and survival among children and adolescents: United States SEER Program 1975–1995,

SEER Program. Bethesda Md: National Cancer Institute, 1999. NIH Publication 99-4649.

16. Eagle RC Jr. High-risk features and tumor differentiation in retinoblastoma: a retrospective histopathologic study. *Arch Pathol Lab Med*. 2009;133(8):1203-1209.

17. Gupta R, Vemuganti GK, Reddy VA, Honavar SG. Histopathologic risk factors in retinoblastoma in India. *Arch Pathol Lab Med.* 2009;133(8):1210-1214.

18. Magramm I, Abramson DH, Ellsworth RM. Optic nerve involvement in retinoblastoma. *Ophthalmology*. 1989;96(2):217-22.

19. Wolff JA, Pratt CB, Sitarz AL. Chemotherapy of metastatic retinoblastoma. *Cancer Chemother Rep*. 1962;16:435-37.

20. Lonsdale D, Berry DH, Holcomb TM, et al. Chemotherapeutic trials in patients with metastatic retinoblastoma. *Cancer Chemother Rep*. 1968;52(6):631-634.

21. Hayman GA, Ellsworth RM, Feind CR, et al. Combination chemotherapy in retinoblastoma. *Arch Ophthalmol.* 1968;80:744-746.

22. White L. Chemotherapy for retinoblastoma: where do we go from here? *Ophthalmic Pediatr Genet.* 1991;12(3):115-130

23. Chan HSL, Gallie BL, Munier FL, Popovic MB. Chemotherapy for retinoblastoma. *Ophthalmol Clin N Am.* 2005;18(1):55-63.

24. Howarth C, Meyer D, Hustu HO, et al. Stage-related combined modality treatment of retinoblastoma: results of a prospective study. *Cancer*. 1980;45(5):851-858.

25. Wolff JA, Boesel CP, Dyment PG et al. Treatment of retinoblastoma: a preliminary report. In: Raybaud C, Clement R, Lebreuil G et al., eds. International Congress Series 570: *Pediatric Oncology*. Proceedings XIIIth Meeting International Society of Pediatric Oncology, Amsterdam; Princeton [N.J.]: Experta Medica ; New York: 1982;364-368.

26. Keith GC. Chemotherapy in retinoblastoma management. *Ophthalmic Pediatr Genet.* 1989;10(2):93-98.

27. Zelter M, Damel A, Gonzalez G, Schwartz L. A prospective study on the treatment of retinoblastoma in 72 patients. *Cancer*. 1991;68(8);1685-1690.

28. Schvartzman E, Chantada G, Fandino A. Results of a stage-based protocol for the treatment of retinoblastoma. *J Clin Oncol.* 1996;14(5):1532-1536.

29. Namouni F, Doz F, Tanguy ML. High-dose chemotherapy with carboplatin, etoposide and cyclophosphamide followed by a hematopoietic stem cell rescue in patients with high-risk retinoblastoma: a SFOP and SFGM study. *Eur J Cancer.* 1997;33(14):2368-2375.

30. Mustafa MM, Jamshed A, Khafaga Y, et al. Adjuvant chemotherapy with vincristine, doxorubicin, and cyclophosphamide in the treatment of postenucleation high risk retinoblastoma. *J Pediatr Hematol Oncol.* 1999;21(5):364-369.

31. Uusitilo MS, van Quill KR, Scott IU, et al. Evaluation of chemoprophylaxis in patients with unilateral retinoblastoma with high-risk features on histopathology examination. *Arch Ophthalmol*. 2001;119(1):41-48.

32. Cuenca A, Giron F, Castro D, et al. Microscopic scleral invasion in retinoblastoma. Clinicopathological features and outcome. *Arch Ophthalmol* 2009; 127(8):1006-1010.

33. Shields CL, Shields JA. Retinoblastoma management: advances in enucleation, intravenous chemoreduction, and intra-arterial chemotherapy. *Curr Opin Ophthalmol.* 2010;21(3):203-212.

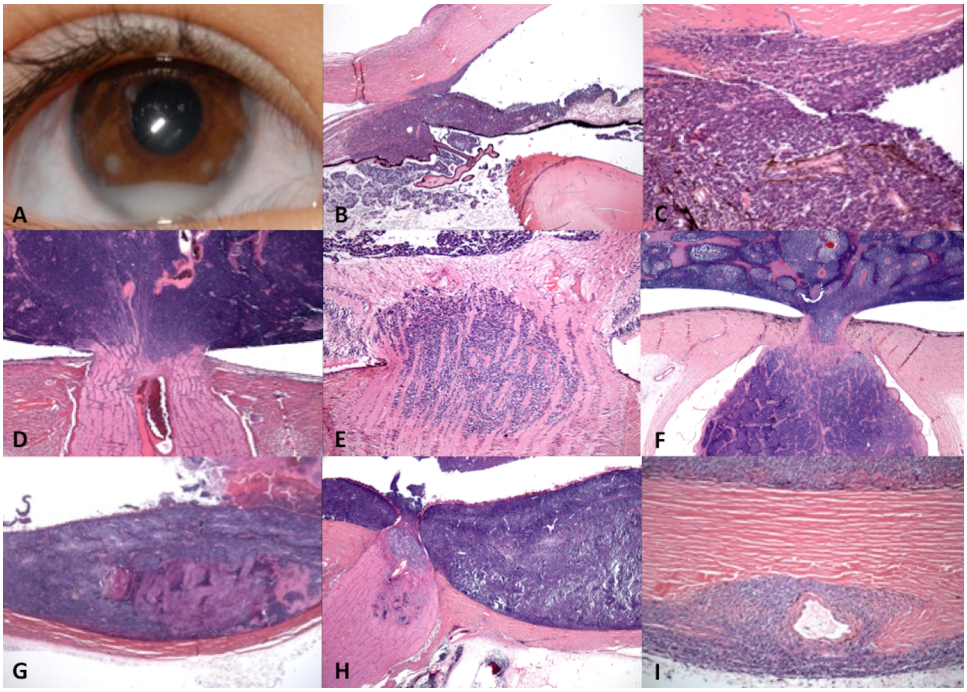

Figure 1:

Successful management of high-risk retinoblastoma using vincristine, etoposide, and carboplatin, illustrating the various degrees of invasive malignancy.

A,B,C. Anterior chamber invasion of retinoblastoma with pseudohypopyon (A) and iris, ciliary body, and trabecular meshwork invasion on 10x magnification (B) and 40x magnification (C).

D, E, F. Tumor invasion into the optic nerve in the pre-laminar (D), laminar (E), and post-laminar (F) region.

G, H, I. Solitary massive choroidal invasion of 16mm (G), combined massive choroidal and optic nerve invasion (H), and massive choroidal invasion with extrascleral extension (I).

Table 1: Postenucleation Adjuvant Chemotherapy in the Treatment of High-Risk Retinoblastoma: Chemotherapeutic regimen[a]

Day	Chemotherapeutic Regimen		
	Vincristine sulfate, 0.05mg/kg	Etoposide phosphate, 5 mg/kg	Carboplatin, 18.6 mg/kg
0	x	x	x
1	…	x	…

[a] The regimen was planned for 4 to 6 cycles.

Demographic feature	Value

Table 2. Demographic Features of 51 Patients Receiving Treatment for High-Risk Retinoblastoma[a]

Age (months)	

Mean (median [range])	42 (28 [4 to 368])
≤ 12 months	9 (18)
> 12 months	42 (82)
Gender	
Male	30 (59)
Female	21 (41)
Race	
Caucasian	35 (69)
African-American	6 (12)
Hispanic	10 (20)
Heredity	
Sporadic	49 (96)
Familial	2 (4)
Genetic testing[b]	
Somatic	9/14 (64)
Germline	5/14 (36)
Laterality	
Unilateral	32 (63)
Bilateral	19 (37)
Eye with high-risk features	
Right	24 (47)
Left	26 (51)
Both	1 (2)

[a]Data are given as number (percentage) of patients unless otherwise specified.

[b]Genetic testing was available in only 14 of 51 patients.

Table 3. Clinical Features at Presentation of 51 Patients Receiving Treatment for High-Risk Retinoblastoma

Clinical feature	Value
Presenting symptom[a]	
Leucocoria	33 (63)
Strabismus	10 (19)
Decreased vision	6 (12)
Blind painful eye	3 (6)
Red eye	2 (4)
Heterochromia	2 (4)
Duration of symptoms, mean (median [range]), days	114 (38 [0 to 730])
History of previous intraocular surgery	

Anterior chamber tap	1 (2)
Vitrectomy with or without scleral buckle	4 (8)
Visual acuity	
Fix and follow	15 (29)
No fix or follow	37 (71)
Intraocular pressure, mean (median [range]), mm Hg	22 (21 [<4 to 50)
Clinical signs	
Secondary Glaucoma	23 (44)
Anterior chamber seeding	16 (31)
Neovascularization iris	22 (42)
Hyphema	4 (8)
Vitreous seeds	37 (71)
Subretinal seeds	12 (23)
Subretinal fluid	16 (31)
Vitreous hemorrhage	8 (15)
Basal diameter of largest tumor, mean (median [range]), mm	20 (21 [10 to 24])
Ultrasonographic thickness, mean (median [range]), mm	12 (13 [3 to 18])

[a]Total may not equal 100% because 4 patients had more than 1 presenting complaint.

Table 4. Histopathologic Features of 51 Patients Receiving Treatment for High-Risk Retinoblastoma

Histopathologic feature	Number (%) of patients
Growth pattern	
Endophytic	12 (23)
Exophytic	6 (12)
Both endophytic and exophytic	27 (52)
Diffuse infiltrating	7 (13)
Tumor differentiation	
Well differentiated	5 (10)
Moderately differentiated	0
Poorly differentiated	43 (83)
Undifferentiated	4 (8)
Necrosis	45 (87)
Dystrophic calcification	48 (92)
Main histopathologic high-risk features	
Anterior segment invasion[a]	7 (13)
Isolated posterior uveal invasion ≥3mm	6 (12)
Isolated postlaminar optic nerve invasion[b]	15 (29)
Any posterior uveal and optic nerve invasion	24 (46)
Total histopathologic high-risk features	

Anterior segment	7 (13)
MUI with no ONI	6 (12)
MUI with non-postlaminar ONI	4 (8)
Combined MUI and postlaminar ONI	3 (6)
Postlaminar ONI and no UI	15 (29)
Postlaminar ONI and nonmassive UI	2 (4)
Combined nonmassive UI and non-postlaminar ONI	15 (29)
Other features	
Iris infiltration	16 (31)
Ciliary body infiltration	12 (23)
Prelaminar optic nerve invasion	6 (12)
Laminar optic nerve invasion	6 (12)
Scleral infiltration	3 (6)
Extrascleral infiltration	1 (2)

Abbreviations: MUI, massive posterior uveal invasion; ONI, optic nerve invasion; UI, posterior uveal invasion.

[a]All patients with anterior chamber seeding had iris and/or ciliary body infiltration.

[b]One patient had invasion up to optic nerve surgical transection.

Table 5: The Role of Adjuvant Chemotherapy in Preventing Metastasis in High-Risk Retinoblastoma: Published Literature[a]

Source	Chemotherapeutic Drugs Used	No. of Patients	Metastasis, No. (%) of Patients
Howarth et al,[29] 1980	V, Cy	14	1 (7%)
Wolff et al,[30] 1981	V, Cy	41	6 (12%)
Keith et al,[24] 1989	V, Cy	26	1 (4%)
Zelter et al,[25] 1991	V, D, Cy	24	8 (33%)
Khelfaoui et al,[9] 1996	Variable**	75	4 (6%)
Schvartzman et al,[31] 1996	V, D, Cy	29	4 (14%)
Namouni et al,[32] 1997	V, Cy, C	6	1 (17%)
Mustafa et al,[26] 1999	V, D, Cy	27	5 (19%)
Uusitalo et al,[27] 2001	Variable**	11	1 (9%)
Honavar et al,[10] 2002	V, D, Cy or V, E, C	46	2 (4%)
Chantada et al,[13] 2004	V, D, Cy or V, I, Cy	24	4 (17%)
Cuenca et al,[33] 2009	Variable**	32	6 (19%)
Present study, 2010	V, E, C	52	0 (0%)

Abbreviations: C, Carboplatin; Cy, cyclophosphamide; D, doxorubicin hydrochloride; E, etoposide; I, Idarubicin hydrochloride; V, Vincristine sulfate.

[a]The number of patients and overall results in some of the studies may be different from the data compiled in the table because only relevant and comparable data are tabulated.

[b]More than 2 regimens were used.