Postenucleation Adjuvant Chemotherapy With Vincristine, Etoposide, and Carboplatin for the Treatment of High-Risk Retinoblastoma

Swathi Kaliki, MD; Carol L. Shields, MD; Sanket U. Shah, MD; Ralph C. Eagle Jr, MD; Jerry A. Shields, MD; Ann Leahey, MD

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

Purpose: To determine the efficacy of postenucleation adjuvant chemotherapy with vincristine, etoposide, and carboplatin 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, postlaminar 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 3 mm 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 extraocular 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, etoposide, and carboplatin in all cases, there was no metastasis during a mean follow-up of 66 months (median [range], 55 [12-202] months).

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

Arch Ophthalmol. 2011;129(11):1422-1427
phate, and carboplatin (VEC) in the prevention of RB metastasis in high-risk cases following enucleation.

**METHODS**

This study was a retrospective, nonrandomized, noncomparative, 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). 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, was recorded. Patients with high-risk RB who received postenucleation adjuvant chemotherapy with 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 or somatic) for RB were recorded when available. The hereditary pattern (sporadic or 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 or bilateral), total number of tumors per eye, International Classification of Retinoblastoma group, Reese-Ellsworth classification, intraocular pressure (millimeters of mercury 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 fovea (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, or 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.

**Figure.** Successful management of high-risk retinoblastoma using vincristine, etoposide, and carboplatin, illustrating the various degrees of invasive malignancy. Anterior chamber invasion of retinoblastoma with pseudohypopyon (A) and iris, ciliary body, and trabecular meshwork invasion on ×10 magnification (B) and ×40 magnification (C). Tumor invasion into the optic nerve in the prelaminar (D), laminar (E), and postlaminar (F) regions. Solitary massive choroidal invasion of 16 mm (G), combined massive choroidal and optic nerve invasion (H), and massive choroidal invasion with extrascleral extension (I).
In patients with high-risk RB, postenucleation 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 and yearly thereafter. 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 patients (10%) had a history of previous intraocular surgery, which included vitrectomy and scleral 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 extracocular invasion 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%).

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 patient (2%). There was no case of etoposide-related leukemia. One patient (2%) had extraocular 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 up 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%) had more than 5 years' follow-up.

The incidence (95% confidence interval) of metastasis was 0% (0%-6%) at 1 year, 0% (0%-7%) at 3 years, and 0% (0%-14%) at 5 years. There was no second malignant neoplasm or death in any case.

### COMMENT

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 associates10 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,6,17 12% to 42% for choroidal invasion,5,8,9,17 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 the postlaminar optic nerve,5,6,8,9,17,18 and 1% to 38% for involvement of the optic nerve to surgical transection.5,8,9,17,18

In a recent comprehensive report on histopathologic findings following enucleation in 297 untreated eyes of RB, Eagle16 identified high-risk features in 55 eyes (18.5%). In these 55 eyes, these features included massive (de-
in high-risk RB and found distant metastasis and subsequent death in 10% of cases. They concluded that alternative chemotherapeutic agents should be considered for patients with such high-risk features. Uusitalo and associates studied 129 patients using variable regimens and concluded that chemoprophylaxis was beneficial in patients with tumor extending beyond the lamina cribrosa. Honavar and colleagues 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 multiagent 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. On the basis of our results, VEC is impressively effective for postenucleation high-risk RB in the prevention of systemic metastases, thereby improving survival.

Submitted for Publication: February 24, 2011; final revision received June 7, 2011; accepted June 8, 2011.

Correspondence: Carol L. Shields, MD, Ocular Oncology Service, Suite 1440, Wills Eye Institute, 840 Walnut St, Philadelphia, PA 19107 (carol.shields@shieldsoncology.com).

Author Contributions: Dr C. L. Shields had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

Funding/Support: Support for this study was provided by the Eye Tumor Research Foundation, Philadelphia, Pennsylvania (Dr C. L. Shields), and the Noel T. and Sara L. Simmonds Endowment for Ophthalmic Pathology, Wills Eye Institute (Dr Eagle).

REFERENCES


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.


