Comparison of Retinoblastoma Reduction for Chemotherapy vs External Beam Radiotherapy

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Objective: To determine the time course and extent of tumor reduction associated with systemic chemotherapy or external beam radiotherapy (EBRT) in the treatment of advanced intraocular retinoblastoma.

Methods: Retrospective review of children with Reese-Ellsworth stages IV and V retinoblastoma undergoing primary globe-conserving therapy with either systemic chemoreduction or EBRT. Study variables were recorded at baseline, at monthly intervals for the first 6 months, and at 12 months after the initiation of treatment. Tumor volumes were calculated using basal area and height values determined by ultrasonography, physical examination, and fundus photographic review.

Main Outcome Measures: Outcome measures included tumor volume, tumor reduction, regression pattern, treatment-related complications, metastases, and survival.

Results: Twenty-six eyes of 26 patients were evaluated for tumor response; 18 patients were treated with systemic chemotherapy and 8 patients were treated with EBRT. Median follow-up was 36 months. A mean 68% reduction in tumor volume occurred after 1 cycle of chemotherapy compared with a 12% reduction at a similar time point (1 month) after initiation of EBRT ($P < .004$). There was no statistically significant difference in tumor volume reduction between treatment modalities at the 12-month follow-up visit. Both systemic chemoreduction and EBRT achieved 100% globe conservation and 100% patient survival in this series.

Conclusions: Retinoblastoma reduction exhibits a differential time course based on the applied primary treatment. Systemic chemotherapy is associated with earlier tumor reduction than EBRT.

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The study protocol was approved by the institutional review board of the University of Miami School of Medicine, Miami, Fla. A retrospective review was performed of medical, photographic, and echographic records of all patients who completed systemic chemotherapy or EBRT as primary treatment of retinoblastoma at the Bascom Palmer Eye Institute, Miami, with complete documentation from October 1, 1991, to May 31, 2001. A total of 175 records was reviewed; 26 patients met the inclusion criteria of the study. Only patients with Reese-Ellsworth stages I, II, and III retinoblastomas were included in the study. Reese-Ellsworth stages IV and V retinoblastomas were included in the study to allow accurate measurement of the tumor size. If more than 1 tumor was present, only the largest tumor at baseline was included in the study. Each patient underwent examination under anesthesia on presentation and at monthly intervals during the follow-up period. Data collected included the patient’s age at diagnosis, family history, Reese-Ellsworth stage at presentation, type of primary treatment (systemic chemotherapy or EBRT), number of cycles of treatment, total dose of radiation, type of adjunctive therapy (laser and/or cryotherapy), calculation of the tumor volume, type of tumor regression pattern, recurrence of the tumor, preservation of the globe, and survival of the patient.

### Table 1. Patient Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Those Who Received Chemotherapy</th>
<th>Those Who Received EBRT</th>
<th>Total</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), mo</td>
<td>9 (11)</td>
<td>17 (15)</td>
<td>11 (12)</td>
<td>.16</td>
</tr>
<tr>
<td>Male</td>
<td>11 (61)</td>
<td>6 (75)</td>
<td>17 (65)</td>
<td>.67</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>9 (50)</td>
<td>6 (75)</td>
<td>15 (58)</td>
<td>.64</td>
</tr>
<tr>
<td>Black</td>
<td>3 (17)</td>
<td>1 (13)</td>
<td>4 (15)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>5 (28)</td>
<td>2 (31)</td>
<td>6 (23)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (6)</td>
<td>0</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Bilateral disease</td>
<td>14 (78)</td>
<td>7 (88)</td>
<td>21 (81)</td>
<td>.99</td>
</tr>
<tr>
<td>Positive family history</td>
<td>8 (44)</td>
<td>0</td>
<td>8 (31)</td>
<td>.03</td>
</tr>
<tr>
<td>R-E stage Vb†</td>
<td>8 (44)</td>
<td>5 (63)</td>
<td>13 (50)</td>
<td>.67</td>
</tr>
</tbody>
</table>

Abbreviations: EBRT, external beam radiotherapy; R-E, Reese-Ellsworth.

†The R-E stage Vb is vitreous seeding.

### Table 2. Primary Therapy

<table>
<thead>
<tr>
<th>Type of Treatment</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Carboplatin, etoposide phosphate, and vincristine sulfate</td>
<td>18 (100)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>9 (50)</td>
</tr>
<tr>
<td>EBRT dose, rad (Gy)</td>
<td></td>
</tr>
<tr>
<td>4320 (43.2)</td>
<td>1 (12)</td>
</tr>
<tr>
<td>4500 (45.0)</td>
<td>7 (88)</td>
</tr>
</tbody>
</table>

Abbreviation: EBRT, external beam radiotherapy.

### Table 3. Adjunctive Therapy

<table>
<thead>
<tr>
<th>Type of Adjunctive Therapy</th>
<th>Those Who Received Chemotherapy</th>
<th>Those Who Received EBRT</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>0</td>
<td>2 (25)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Diode laser</td>
<td>9 (50)</td>
<td>1 (13)</td>
<td>10 (39)</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>0</td>
<td>2 (25)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Diode laser + cryotherapy</td>
<td>9 (50)</td>
<td>3 (38)</td>
<td>12 (46)</td>
</tr>
</tbody>
</table>

Abbreviation: EBRT, external beam radiotherapy.

*Data are given as the number (percentage) of patients.

All patients in the chemoreduction arm of the study received carboplatin (20 mg/kg for patients younger than 12 months; 550-600 mg/m² body surface area for patients older than 12 months), etoposide phosphate (5 mg/kg if the patient was younger than 12 months; 150 mg/m² body surface area if the patient was older than 12 months), and vincristine sulfate (0.05 mg/kg if the patient was younger than 12 months; 1.5-2 mg/m² body surface area if the patient was older than 12 months). For patients also receiving cyclosporine, cyclosporine was administered as a 5 mg/kg per hour bolus for 2 hours before chemotherapy started, then a 1.5 mg/kg per hour infusion during the next 30 hours if the patient weighed less than 12 kg. These doses were adjusted to 4 mg/kg per hour and 1.25 mg/kg per hour, respectively, if the patient weighed between 12 and 30 kg, or 3 mg/kg per hour and 1 mg/kg per hour, respectively, if the patient weighed more than 30 kg.20 External beam radiotherapy was administered using the relative lens-sparing technique and included treatment to the 95% isodose line, with a goal dose of 4500 rad (45 Gy) of megavoltage radiation at 180 rad (1.8 Gy) per fraction.3

### CALCULATION OF TUMOR VOLUME

Echographic analysis was performed using an ultrasonic scanner (model 1; Innovative Imaging Inc, Sacramento, Calif) or the Alcon Ophthalmoscans or the Mini A Systems (Alcon Surgical, Irvine, Calif). Baseline echographic measurements of all tumors were obtained while the patient was anesthetized at the initial examination. Measurement of the maximal tumor height was determined from baseline B-scan sections.

Kowa photographs (Kowa Optimed Inc, Torrance, Calif) and/or Retcam 120 images (Massie Research Laboratories Inc, Dublin, Calif), obtained at the initial presentation and at each follow-up examination, were used for photographic analysis. A digital montage of Kowa images was created using a slide scanner (model LS-2000; Nikon Corp, Tokyo, Japan) and photographic montaging software (Sketcher 3.0; Ophthalmic Technologies Inc, Toronto, Ontario). Montage images displayed borders of tumor and included images of the optic disc for reference. Measurement of the tumor length, width, and basal area were determined from photographic analysis using caliper measurements and were internally validated using the optic disc as a reference (1.3 mm in diameter). Tumor surface areas in Retcam 120 images were obtained using the Retcam software that enabled us to calculate tumor surface area after outlining the margins of the tumor.

Tumor volumes were calculated using radius, basal area, and height values as determined by ultrasonographic, photographic, and physical examination. The following formula was used for the calculation of the tumor volume

\[ \text{Volume} = \left(\frac{1}{3} \times \pi \times \text{height}^2\right) \times (3 \times \text{radius} - \text{height}) \]

This formula allows increased accuracy in quantifying intraocular tumor volumes.20

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Percent change in tumor area and volume were calculated at 1-, 2-, 3-, 4-, 5-, 6-, and 12-month intervals. If a patient had multiple tumors, only the largest tumor was tracked for volume reduction. The accuracy of data was verified through evaluations by multiple investigators (E.E.B., M.S.B., and T.G.M.) who were masked to treatment modality.

STATISTICAL ANALYSIS

Statistical significance was assessed using the Fisher exact test or the McNemar test for categorical variables and the 2-sample *t* test for continuous variables.

RESULTS

Twenty-six eyes of 26 patients with retinoblastomas were evaluated. Seventeen patients (65%) were male; 9 patients (35%) were female. Bilateral tumors were present in 21 patients (81%); 8 patients (31%) had a positive family history of retinoblastoma. Mean age at presentation was 11 months (age range, 6 days to 49 months). Eighteen patients (69%) received systemic chemotherapy; 8 patients (31%) received EBRT. Mean follow-up was 35 months (follow-up range, 6-72 months). Thirteen patients (50%) were initially seen with Reese-Ellsworth stage Vb disease (ie, with vitreous seeding). Demographic data are summarized in Table 1.

Systemic chemotherapy with a combination of carboplatin, vincristine, and etoposide with or without cyclosporine was given every 3 weeks to a goal of 9 cycles (mean, 7 cycles). Nine patients (50%) treated with systemic chemotherapy received cyclosporine. External beam radiotherapy was delivered in a single daily fractionation over an approximate 3-week interval to a goal dose of 45 000 rad (450 Gy). Primary therapy data are listed in Table 2.

All of the patients treated with systemic chemotherapy (18 of 18 patients) received adjunctive transpupillary diode laser therapy applied at the time of examination administered under anesthesia immediately before the cycles of systemic chemotherapy. In addition, 9 (50%) of 18 patients received adjunctive cryotherapy during an examination under anesthesia. Six of the 8 patients treated with EBRT received cryotherapy, transpupillary diode laser therapy, or both during an examination under anesthesia. Adjunctive treatment data are given in Table 3.

Patient survival was 100%, none of the patients developed metastases at the last follow-up, and there was a 100% globe conservation rate.

There was a statistically significant difference in tumor volume reduction between systemic chemotherapy and EBRT at the first (*P* < .004) and second (*P* < .04) months after the initiation of therapy (Figure 1). Patients treated with systemic chemotherapy had a tumor volume 32% of baseline (68% reduction from baseline) while those patients treated with EBRT had a tumor volume 88% of baseline (12% reduction from baseline) at the first-month follow-up visit. The difference in rate of tumor volume reduction persisted but gradually decreased until the 12-month follow-up visit, when the tumor volume reduction was noted to be similar between the 2 groups (*P* = .76) (Figure 2). Data for tumor volume changes are listed in Table 4.

Local treatment-related complications are given in Table 5. Posterior subcapsular cataract was present in 7 of 26 patients, vitreous hemorrhage in 4 of 26 patients, and midfacial hypoplasia in 2 of 26 patients. Cataracts (7 of 8 patients) and midfacial hypoplasia (2 of 8 patients) developed exclusively in patients treated with EBRT (*P* < .001 and *P* < .09, respectively). There was no significant difference in any other local treatment-related complication, including retinal vasculopathy and optic neuropathy.

COMMENT

Systemic chemotherapy and EBRT with adjunctive laser, cryotherapy, or both are associated with significant retinoblastoma volume reduction. In the current study, patients treated with primary systemic chemoreduction...
exhibited an earlier reduction of tumor volume than those treated with EBRT.

Early reduction in tumor size is vital to the successful treatment of retinoblastoma; reduction in tumor volume allows for effective application of local treatments, leading to tumor control. Visual compromise depends on tumor size and extent of foveal involvement.23 Faster reduction in tumor volume and partial reduction in foveal involvement may allow for improved visual acuity outcomes and decreased amblyopia and strabismus given the plasticity of the pediatric visual system.

In this study, calculations of change in volume between consecutive follow-up examinations were based on the change in tumor size as observed clinically and in fundus photographs in addition to echographic measurements. Char et al26 have demonstrated the relative inaccuracy of such clinical estimations in assessing tumor dimensions when compared with more conventional modalities such as echography.

We postulate that direct laser ablation coupled with concomitant systemic chemotherapy leads to a rapid direct tumor cell death, enhanced vascular closure, and a potential synergy of each individual modality. External beam radiotherapy has been previously documented to achieve tumor control through direct tumoricidal effects.27 Radiotherapeutic effects though may not be immediately apparent as cell death is initiated through DNA damage often not manifested until cell cycling. External beam radiotherapy has also been associated with transient tumor enlargement with local intratumoral edema.7

Globe-conservation rates in the present study were 100% in both groups. This compares favorably with previously published results. Scott et al8 reported 91% globe conservation at 36 months using the relative lens-sparing technique of EBRT for patients with Reese-Ellsworth stages I through Vb disease. Egbert et al28 reported 29% ocular survival following therapy with lateral beam EBRT on patients with Reese-Ellsworth stages IV and V retinoblastomas with a follow-up range of 2.5 to 21 years. Shields et al29 reported 100% and 78% ocular salvage rates when a chemotherapeutic regimen consisting of a combination of carboplatin, vincristine, and etoposide with adjuvant treatment was used on stages IV and V retinoblastomas, respectively.29 In this study, the 100% globe-conservation rate was likely affected favorably by the exclusion of patients undergoing primary enucleation. Furthermore, outcomes may have been favorably influenced by the small sample size.

In patients undergoing treatment with systemic chemoreduction or EBRT for retinoblastoma, adjuvant local treatments with laser and cryotherapy are valuable in controlling tumor growth. Laser and cryotherapy play a role in speeding the rate of regression of these tumors. Our laboratory has previously reported that application of focal adjunctive therapies to retinoblastomas at the time of systemic chemotherapeutic dosing or radiation therapy increases the efficacy of the systemic chemoreductive agents and allows for a reduction in total ocular and periocular radiation dose while maintaining excellent local tumor control in the murine model of retinoblastoma.30-32 It has been demonstrated that multagent chemotherapy alone does not ensure intraocular control for multifocal retinoblastoma. Thus, supplemental focal treatment may be needed to control disease progression.33 Focal ablative therapies may cause complications including transient ablatio fugax, retinal vascular occlusion, retinal holes, preretinal fibrosis, and retinal traction and tears.34 In this study, all patients receiving chemotherapy also received adjuvant therapy. Fifty percent of these patients re-
ceived laser therapy; the remaining 50% were treated with a combination of laser and cryotherapy. Two patients treated with EBRT received no adjuvant treatment. The small sample size of patients receiving no adjuvant treatment in this study precluded comparative analysis in outcomes between patients receiving adjuvant treatments and those not receiving adjuvant treatment.

An important goal in the treatment of retinoblastoma is to achieve local tumor control and globe conservation while minimizing treatment-related morbidity. Adjuvant therapies combined with primary treatment modalities have achieved tumor control in human subjects. In low-risk patients with other neurologic tumors (eg, medulloblastoma), adjuvant chemotherapy allows for dose reduction of irradiation, which results in improved quality of life and fewer radiation-related complications. Further refinement of current therapies and development of new treatments for retinoblastoma should continue the trend toward combination therapy and allow for dose reduction and minimization of treatment-related morbidity.

External beam radiotherapy can lead to significant local adverse effects. In the present study, 7 (88%) of 8 eyes treated with EBRT developed posterior subcapsular cataracts; none of the chemotherapy-treated eyes developed cataracts. Two (25%) of 8 patients treated with EBRT developed midfacial hypoplasia, while none of the chemotherapy-treated patients developed facial abnormalities. Treatment of retinoblastoma with systemic chemotherapy appears to be less likely to result in significant local adverse effects than treatment with EBRT.

Systemic complications of EBRT include late tumor development at distant sites, including osteogenic sarcomas and rhabdomyosarcomas. Systemic chemoreduction is a relatively new treatment strategy for retinoblastoma; for this reason, it is difficult to assess the likelihood of late secondary tumors in this patient group. None of the patients included in this study developed local secondary tumors, but the longest follow-up was only 72 months. We have previously reported the significant adverse effects, such as myelosuppression, associated with treatment of retinoblastoma with systemic chemotherapy. Although myelosuppression is a known complication of systemic chemoreduction, this end point was not evaluated. When used as primary treatment of retinoblastoma, both EBRT and systemic chemotherapy are associated with significant systemic adverse effects.

Both systemic chemotherapy and EBRT achieve excellent tumor control, globe conservation, and patient survival. However, the faster tumor response noted in patients undergoing systemic chemotherapy as well as the decreased chance for local treatment–related adverse effects has led us to prefer systemic chemotherapy as our primary treatment option for advanced retinoblastoma.

To avoid the systemic treatment–related morbidity associated with both systemic chemotherapy and EBRT, our laboratory and other laboratories have been investigating the use of local delivery of chemotherapeutic and antiangiogenic agents in the treatment of retinoblastoma. As with systemic chemotherapy, the goal of these proposed treatments will be to reduce retinoblastoma volume so that the tumors will be amenable to local treatments with laser and cryotherapy. The time course of tumor volume reduction and treatment-associated morbidity of these newer, local primary therapies will need to be compared with systemic chemotherapy to provide optimum therapeutic intervention and to minimize adverse effects.

Retinoblastoma reduction exhibits a differential time course and extent based on the applied primary treatment. Systemic chemotherapy is associated with earlier tumor volume reduction than EBRT. Combined application of multiple treatment modalities may enhance tumor reduction and accelerate the time course of tumor response.

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