The Outcome of Chemoreduction Treatment in Patients With Reese-Ellsworth Group V Retinoblastoma

Kaan Gündüz, MD; Carol L. Shields, MD; Jerry A. Shields, MD; Anna T. Meadows, MD; Nicole Gross, MD; Jacqueline Cater, PhD; Michael Needle, MD

Objective: To determine the outcome of chemoreduction treatment in patients with Reese-Ellsworth group V retinoblastoma.

Methods: Prospective analysis of 27 eyes in 22 patients with group V retinoblastoma treated with either 2- or 6-cycle chemoreduction and focal treatment methods (argon laser photocoagulation, transpupillary thermotherapy, cryotherapy, and plaque radiotherapy). The need for external beam irradiation and the eventual globe salvage rate were assessed. Median follow-up was 28 months.

Results: There were 16 eyes in the 2-cycle chemoreduction treatment group and 11 eyes in the 6-cycle chemoreduction treatment group. No significant difference was noted between the 2 groups with respect to baseline patient and eye findings. After chemoreduction treatment, external beam irradiation was necessary in 12 (75%) of 16 eyes in the 2-cycle chemoreduction treatment group and in 4 (36%) of 11 eyes in the 6-cycle chemoreduction treatment group. There was no statistical difference between the 2- and 6-cycle chemoreduction treatment groups with respect to necessity for external beam irradiation (logistic regression analysis). All 4 eyes in the 2-cycle chemoreduction treatment group and 3 of 12 eyes in the 2-cycle chemoreduction treatment and irradiation group were eventually enucleated, the globe salvage rates being 0% and 75%, respectively. Two of 7 eyes in the 6-cycle chemoreduction treatment group and 1 of 4 eyes in the 6-cycle chemoreduction treatment and irradiation group were enucleated, the globe salvage rates being 71% and 75%, respectively. Except for the 2-cycle chemoreduction treatment group, in which the globe salvage rate was significantly lower (P = .03), there was no difference among the other 3 groups (2-cycle chemoreduction treatment and irradiation, 6-cycle chemoreduction treatment, and 6-cycle chemoreduction treatment and irradiation) with respect to globe salvage (logistic regression analysis).

Conclusions: Local tumor control of group V retinoblastoma is possible with 6-cycle chemoreduction and focal therapy when external beam irradiation is not used. A larger sample size is necessary to determine how often external beam irradiation can be avoided.


The Reese-Ellsworth classification was introduced as a method of assessing the extent of ocular involvement and predicting globe salvage in eyes with retinoblastoma. Eyes with retinoblastoma having massive tumors involving more than half of the retina are classified as Reese-Ellsworth group Va disease. The presence of vitreous seeding, often in the presence of advanced intraocular disease, is usually classified as Reese-Ellsworth group Vb disease.

Systemic chemotherapy was initially used in the treatment of patients with extraocular retinoblastoma involving the optic nerve, choroid, and orbit or with distant metastasis. Recently, several reports have been published on chemoreduction treatment, usually combined with adjuvant therapies, for the management of intraocular retinoblastoma. In a pilot study, it was found that after 2-cycle chemoreduction treatment there was a 35% reduction in tumor base and a 49% reduction in tumor thickness. Use of chemoreduction provided reduction of tumor size so that focal methods could be used to treat the residual tumor. Chemoreduction has been used either singly or in combination with other treatment methods in patients with group I through III tumors and in some patients with more advanced disease, including group IV and V tumors. However, the question is still not answered as to whether chemoreduction should be used in patients with group V retinoblastoma or whether such eyes should be managed by external beam irradiation or enucleation without chemoreduction treatment.
PATIENTS AND METHODS

We prospectively analyzed data on 27 eyes in 22 consecutive patients with Reese-Ellsworth group V retinoblastoma treated with chemoreduction in the Oncology Service at Wills Eye Hospital, Philadelphia, Pa, between August 1994 and July 1996. Children with group V retinoblastoma in 1 or both eyes were eligible for this study, except those with iris neovascularization or tumor invasion into the pars plana, anterior chamber, choroid, orbit, or optic nerve as determined by results of clinical, ultrasonographic, and neuroimaging studies. These patients were generally treated by enucleation. Patients with systemic involvement or any previous treatment for retinoblastoma and those with liver, kidney, or ear problems were also excluded. Informed consent was obtained before treatment.

Baseline patient data included age at diagnosis, sex, and hereditary pattern of the tumor (sporadic or familial). Ocular examination findings were assessed for laterality, total number of tumors per eye, Reese-Ellsworth classification, largest tumor diameter (in millimeters using indirect ophthalmoscopy), thickness (in millimeters measured by A-scan and B-scan ultrasonography), the presence of subretinal fluid, and tumor seeding in the vitreous and subretinal space.

The chemotherapy drugs used in the protocol included intravenous carboplatin, etoposide phosphate, and vincristine sulfate. Treatment duration was either 2 or 6 months (Table 1 and Table 2). Chemotherapy was administered at the Children’s Hospital of Philadelphia by 1 of us (A.T.M.).

Ocular examination was performed under anesthesia every month until maximum regression and stabilization of the disease was achieved. When maximum tumor regression was achieved, a decision regarding focal treatment to the regressed retinal tumor, vitreous seeds, and subretinal seeds was made. The focal treatment methods included argon laser photocoagulation, transpupillary thermotherapy, cryotherapy, and plaque radiotherapy. When retinal tumor or seed control could not be achieved with these methods, the options of external beam irradiation and enucleation were considered. Although we had general guidelines for the choice of enucleation and external beam irradiation, the indications sometimes were not clear-cut.

External beam irradiation was considered for patients with persistent or recurrent retinal tumors larger than 12 mm in base and 8 mm in thickness, multifocal recurrent tumors, vitreous seeds (>2 quadrants), and subretinal seeds (>2 quadrants). Enucleation was generally performed in eyes with persistent or recurrent tumors larger than 20 mm in base and 10 mm in thickness, large multifocal recurrent tumors, vitreous seeds (>2 quadrants), subretinal seeds (>2 quadrants), concern for optic nerve or choroidal invasion, vitreous herniation, iris neovascularization, and neovascular glaucoma. In some patients, enucleation was performed after failure of previous external beam irradiation. In some others, it was done at the family’s request after failure of chemoreduction and focal treatment without resorting to external beam irradiation.

RESULTS

There were 13 patients (7 boys and 6 girls) with 16 affected eyes in the 2-cycle chemoreduction treatment group and 9 patients (5 boys and 4 girls) with 11 affected eyes in the 6-cycle chemoreduction treatment group. Median age at diagnosis was 11 months (mean, 16 months; range, 2-46 months) in the 2-cycle chemoreduction treatment group and 12 months (mean, 18 months; range, 3-42 months) in the 6-cycle chemoreduction treatment group. Table 3 shows the baseline ocular findings. There was no statistical difference between the 2 groups with respect to patient demographics such as age, sex, laterality, and ocular findings (including Reese-Ellsworth group), total number of tumors, largest tumor diameter, tumor thickness, subretinal fluid, vitreous seeds, and subretinal seeds. Analysis of variance and Wilcoxon tests were performed for continuous variables, such as age and tumor diameter, and the Fisher exact test was used for discrete variables, such as number of tumors. The 2 groups, therefore, had differences.

In this study, we aim to document our experience with chemoreduction treatment in patients with Reese-Ellsworth group V retinoblastoma. We initially used 2-cycle chemoreduction treatment and later used 6-cycle chemoreduction treatment under a separate protocol. We analyzed the outcome of patients treated with 2-cycle vs 6-cycle chemoreduction in terms of avoiding external beam irradiation and enucleation.

<p>| Table 1. Chemoreduction Regimen for Patients With Intraocular Retinoblastoma Receiving 2 Cycles of Chemotherapy* |</p>
<table>
<thead>
<tr>
<th>Day</th>
<th>Vincristine</th>
<th>Etoposide</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The regimen is repeated every 3 to 4 weeks twice. The drugs were given in the following doses: vincristine sulfate, 1.5 mg/m² (0.05 mg/kg for children ≤36 months of age; maximum dose, 2 mg); etoposide, 150 mg/m² (5 mg/kg for children ≤36 months of age); and carboplatin, 560 mg/m² (18.6 mg/kg for children ≤36 months of age). Ellipses indicate the drug is not given on that day.

<p>| Table 2. Chemoreduction Regimen for Patients With Intraocular Retinoblastoma Receiving 6 Cycles of Chemotherapy* |</p>
<table>
<thead>
<tr>
<th>Day</th>
<th>Vincristine</th>
<th>Etoposide</th>
<th>Carboplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

*The regimen is repeated every 3 to 4 weeks 6 times. The drugs were given in the following doses: vincristine sulfate, 1.5 mg/m² (0.05 mg/kg for children ≤36 months of age; maximum dose, 2 mg); etoposide, 150 mg/m² (5 mg/kg for children ≤36 months of age); and carboplatin, 560 mg/m² (18.6 mg/kg for children ≤36 months of age). Ellipses indicate the drug is not given on that day.
compared baseline characteristics. Median follow-up was 25 months (mean, 24 months; range, 20-32 months).

After chemoreduction treatment, external beam irradiation was necessary in 12 (75%) of 16 eyes in the 2-cycle chemoreduction treatment group and in 4 (36%) of 11 eyes in the 6-cycle chemoreduction treatment group. External beam irradiation was used more frequently in the 2-cycle compared with the 6-cycle chemoreduction treatment group, although the difference was not statistically significant ($P = .28$, logistic regression analysis).

All 4 eyes in the 2-cycle chemoreduction treatment group were eventually enucleated because of persistent tumor and seeds (3 eyes) and vitreous hemorrhage (1 eye) (Table 4). Three of 12 eyes in the 2-cycle chemoreduction treatment and irradiation group were enucleated because of recurrent tumor and seeds. Two eyes had retinal tumor and subretinal seed recurrence and 1 eye had vitreous seed recurrence. The median interval to retinal tumor and subretinal seed recurrence was 7 months, and the interval to vitreous seed recurrence was 10 months. The globe salvage rate was 0% in the 2-cycle chemoreduction treatment group and 75% in the 2-cycle chemoreduction treatment and irradiation group.

Two of 7 eyes in the 6-cycle chemoreduction treatment group were enucleated after chemoreduction treatment because of nonresponsive advanced intraocular disease (1 eye) and vitreous hemorrhage (1 eye) (Table 4). One of 4 eyes in the 6-cycle chemoreduction treatment and irradiation group was treated with enucleation after external beam irradiation because of vitreous seed recurrence. The interval to vitreous seed recurrence was 11 months. The globe salvage rate was 71% in the 6-cycle chemoreduction treatment group and 75% in the 6-cycle chemoreduction treatment and irradiation group.

Except for the 2-cycle chemoreduction treatment group, in which the globe salvage rate was significantly lower ($P = .03$), there was no difference among the other 3 groups (2-cycle chemoreduction treatment and irradiation, 6-cycle chemoreduction treatment, and 6-cycle chemoreduction treatment and irradiation) with respect to globe salvage (logistic regression analysis).

Overall, of 27 eyes undergoing either 2- or 6-cycle chemoreduction treatment, 16 eyes (59%) received external beam irradiation. Ten eyes were eventually enucleated, the globe salvage rate being 63%. The median external beam radiation dose was 3800 cGy. There were no major adverse effects from the administration of chemoreduction. The only complication was transient myelosuppression, noted in 8 (36%) of 22 patients.

### Table 4. Outcome of 2- and 6-Cycle Chemoreduction and Focal Treatment With and Without External Beam Irradiation in Terms of the Eventual Need for Enucleation

<table>
<thead>
<tr>
<th>Treatment Enucleation, No.</th>
<th>2-Cycle chemoreduction and focal treatment (n = 4 eyes)</th>
<th>6-Cycle chemoreduction and focal treatment (n = 7 eyes)</th>
<th>2-Cycle chemoreduction and focal treatment and external beam irradiation (n = 12 eyes)</th>
<th>6-Cycle chemoreduction and focal treatment and external beam irradiation (n = 4 eyes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

The traditional management of eyes with Reese-Ellsworth group V retinoblastoma has been treatment with either enucleation or external beam radiation. Historically, the globe salvage rate for group V retinoblastoma was limited to 8% to 35%, based on the available treatment methods of external beam irradiation and enucleation. Hungerford et al reported the success rate of primary radiotherapy in eyes with group V retinoblastoma as 45%. However, the overall globe salvage rate after external beam irradiation and focal therapy, including cryotherapy, laser photocoagulation, and plaque radiotherapy, increased to 66%.

Results of several studies of chemoreduction treatment of intraocular retinoblastoma demonstrate varying success with group V eyes. Murphree et al found that most small intraocular retinoblastomas (groups I-III) were curable by chemoreduction and focal treatment. However, in most eyes with large tumors and diffuse vitreous and subretinal seeds (groups IV and V), chemoreduction and focal treatments were not sufficient to eradicate the disease, and external beam irradiation was eventually required.

Kingston and coworkers specifically analyzed the outcome of chemoreduction treatment in patients with group V retinoblastoma. They found that in most patients, external beam irradiation was necessary as an adjunct to chemoreduction treatment. The overall globe salvage rate with combination chemoreduction treatment (2 cycles) and external beam irradiation was 70%, not significantly different from the previously reported salvage rate with external beam irradiation and focal treatment. They concluded that administration of chemoreduction did not significantly reduce the need for external beam irradiation or the eventual rate of enucleation in patients with advanced retinoblastoma. Based on these findings, Kingston et al speculated that chemo-
therapy plus radiotherapy may have toxic effects on the retina and that perhaps a longer period of chemotherapy (6 courses) was necessary to avoid external beam irradiation.

Gallie et al, on the other hand, reported an 83% globe salvage rate with group V retinoblastoma eyes after chemoreduction treatment in combination with cyclosporine and focal treatment. Of 18 group V eyes in their study, 2 (11%) were treated with radiation, 1 of which was subsequently enucleated, and 3 others were enucleated without irradiation.

In a recent report, Shields and associates also found that group V retinoblastoma was potentially treatable with chemoreduction and focal treatment. They reported that at a median follow-up of 12 months, 53% of eyes with Reese-Ellsworth group V retinoblastoma required external beam irradiation after initial chemoreduction treatment, and the globe salvage rate was 78%. With longer follow-up (median, 25 months), we found in the present study that external beam irradiation was necessary in 59% of eyes with group V retinoblastomas, and the overall globe salvage rate was 63%. In addition, Shields et al demonstrated that eyes with advanced intraocular disease and retinal detachment often benefit from chemoreduction treatment, the retina being completely reattached in 76% of eyes after chemoreduction treatment.

Our results show that there are no group V eyes controlled with 2-cycle chemoreduction and adjuvant treatment alone without external beam irradiation. However, there are 5 group V eyes in which local disease and seeds were controlled with 6-cycle chemoreduction and focal treatment without external beam irradiation. These results suggest that in patients with group V eyes, 6-cycle chemoreduction treatment followed by selective focal treatment may be necessary if external beam irradiation is to be avoided, similar to results of previous reports.

Use of external beam irradiation and chemotherapy have been documented to cause second malignant neoplasms in patients with retinoblastoma and other cancers. In patients with bilateral retinoblastoma, the 30-year cumulative incidence of developing second tumors was approximately 35% for those who received external beam irradiation vs 6% for those who did not receive irradiation. In a recent report, patients with bilateral retinoblastoma who underwent external beam irradiation before age 12 months were at higher risk of developing second tumors in the field of radiation compared with those receiving external beam irradiation after age 12 months. In view of this and other effects of irradiation, chemotherapy has been proposed as the primary treatment in patients with retinoblastoma. The risk of developing second tumors with chemotherapy is thought to be less compared with external beam irradiation. The use of etoposide has been reported to be associated with the development of leukemia at doses greater than those used to treat retinoblastoma. Although follow-up is relatively short, we did not observe any serious adverse effects from use of the 3 chemotherapeutic agents, except for transient myelosuppression similar to previous reports. None of the patients developed second or metastatic cancers during follow-up.

Our study results should be interpreted with caution. Although this is a prospective study, it is nonrandomized and there could have been bias in patient assignment. However, there was no statistically significant difference between the 2- and 6-cycle groups with respect to baseline patient characteristics. Second, not all group V eyes were treated with chemoreduction. During the study, we treated 48 eyes with retinoblastoma by primary enucleation, all of which were group V eyes. These were generally unilateral sporadic cases displaying advanced disease, with extensive subretinal and vitreous seeds. The presence of iris neovascularization, neovascular glaucoma, and vitreous hemorrhage in the unequivocal presence of an active retinoblastoma were other indications for enucleation. When there was concern for optic nerve and choroidal invasion, we again resorted to enucleation as the primary treatment. Third, longer follow-up is necessary to assess the ultimate retinal tumor control, seed control, ocular salvage rate, and life prognosis. Although most retinoblastomas demonstrate recurrence in the first year after treatment, as shown in our study, late recurrence can also occur. Fourth, a larger sample size is required to note small to modest effects. In our study, there was no statistical difference between the 2- and 6-cycle chemoreduction treatment groups with respect to avoiding external beam irradiation. However, with a larger sample size, the difference may become statistically evident.

In conclusion, the results of our study indicate that 6-cycle chemoreduction treatment is more effective than 2-cycle chemoreduction treatment for control of group V retinoblastoma. Some patients do well with 6-cycle chemoreduction and focal treatment alone, thereby avoiding external beam irradiation and enucleation. However, external beam irradiation or enucleation should be considered in eyes with advanced residual or recurrent tumor in the retina, vitreous, or subretinal space after chemoreduction treatment.

Accepted for publication August 11, 1998.

This study was supported by the Macula Foundation, New York, NY (Drs Gündüz and C. L. Shields); the Pennsylvania Lions Sight Conservation and Eye Research Foundation, Philadelphia (Drs Gündüz, C. L. Shields, and J. A. Shields); and the Eye Tumor Research Foundation (Dr C. L. Shields) and the Paul Kayser International Award of Merit in Retina Research (Dr J. A. Shields), Houston, Tex.

Reprints: Carol L. Shields, MD, Oncology Service, Wills Eye Hospital, 900 Walnut St, Philadelphia, PA 19107.

REFERENCES


