Chemoreduction for Retinoblastoma May Prevent Intracranial Neuroblastic Malignancy (Trilateral Retinoblastoma)

Carol L. Shields, MD; Anna T. Meadows, MD; Jerry A. Shields, MD; Cynthia Carvalho, MD; Andrew F. Smith, PhD

Objective: To evaluate whether neoadjuvant intravenous chemotherapy (chemoreduction) for retinoblastoma reduces the risk for associated intracranial neuroblastic tumor (trilateral retinoblastoma).

Design: Retrospective consecutive case series.

Participants: Two hundred fourteen consecutive children with newly diagnosed retinoblastoma treated at a major ocular oncology center from January 1, 1995, to July 1, 1999.

Main Outcome Measure: Development of associated intracranial neuroblastic tumor (trilateral retinoblastoma).

Results: During the 54-month study period, 142 patients (66%) received chemoreduction (consisting of vincristine sulfate, etoposide phosphate, and carboplatin therapy) as part of their treatment strategy (chemoreduction group), whereas 72 (34%) were treated with nonchemoreduction methods (nonchemoreduction group). In the chemoreduction group, no associated intracranial neuroblastic tumor developed during the mean 47-month follow-up. Based on a recent meta-analysis of the prevalence of trilateral retinoblastoma, we would have expected the intracranial tumor to develop in 5 to 15 patients with hereditary retinoblastoma. This lack of associated trilateral retinoblastoma in the chemoreduction group was significantly less than expected using binomial distribution \((P<.001)\). In the nonchemoreduction group, associated intracranial tumor (pinealoblastoma) developed in 1 patient, a finding consistent with the expected frequency.

Conclusion: Chemoreduction protects against the highly fatal associated intracranial neuroblastic tumor (trilateral retinoblastoma). This observation is especially important in children with bilateral or familial retinoblastoma who are at greatest risk for this brain tumor.


TRILATERAL retinoblastoma is the association of retinoblastoma and primary intracranial neuroblastic malignancy.\(^1\) This association was first recognized in 1977\(^2\) and later termed \textit{trilateral retinoblastoma} to indicate bilateral intraocular tumors combined with intracranial tumor of similar histopathologic features.\(^3\) The intracranial tumor has been found in the region of the pineal gland most often, but involvement in the parasellar and suprasellar regions have also been recognized.\(^3,5\) Trilateral retinoblastoma is found in approximately 3% of all children with retinoblastoma. These tumors generally develop before patients are 4 years of age.\(^6\) Patients with bilateral or familial retinoblastoma are at greatest risk, with expected development of this intracranial malignant neoplasm in 5% to 15%.\(^4,6\) Some unilateral cases with a germinal mutation may also manifest this tumor.

Previous reports have described the clinical variations, neuroimaging results, treatment, and prognosis in children with this syndrome.\(^6,9\) In children with retinoblastoma who undergo computed tomography or magnetic resonance imaging of the brain, the tumor is usually detected within 1 year of the diagnosis of retinoblastoma and nearly always before 4 years of age.\(^4,10\) Unfortunately, the brain malignancy is commonly fatal and is a major cause of mortality in the first 5 years after diagnosis of bilateral retinoblastoma.\(^9\)

During the past 5 years, we have recognized that development of an intracranial neuroblastic tumor (trilateral retinoblastoma) occurred in fewer of our patients with retinoblastoma, and this was especially apparent in patients treated with neoadjuvant intravenous chemotherapy (chemoreduction) for intraocular retinoblastoma.\(^11,12\) Herein, we report these observations in greater detail.
PATIENTS AND METHODS

We reviewed and included in this analysis the medical charts of all patients with newly diagnosed retinoblastoma that was managed at the Ocular Oncology Service of Wills Eye Hospital, Philadelphia, Pa, from January 1, 1995, through July 1, 1999. The medical charts were evaluated for patient age at diagnosis, race, sex, family history of retinoblastoma, and generation affected with retinoblastoma. The data were reviewed for tumor laterality, classification based on the Reese-Ellsworth system, race, sex, family history of retinoblastoma, and race. All patients with retinoblastoma and 4 with unilateral familial disease. Based on this analysis, 214 children with newly diagnosed retinoblastoma were included in this analysis. The patients were reviewed in 1 of 2 mutually exclusive groups, i.e., chemoreduction or nonchemoreduction, depending on whether they received chemoreduction therapy at any point during their treatment. In each group, separate analyses were performed for patients with bilateral and/or familial retinoblastoma (i.e., at-risk patients), patients with unilateral retinoblastoma, and all patients with retinoblastoma. The development of pineal tumor or other intracranial neuroblastic tumor was recorded.

To determine the statistical significance of the observed values for the occurrence of trilateral retinoblastoma, the data were entered into a binomial distribution formula supplied using commercially available software (Excel, Word 97; Microsoft Corporation, Redmond, Wash), which simultaneously examines the number of successes in the trial, defined as those instances where the event of interest occurs (in this case the number of observed trilateral retinoblastoma cases), the number of independent trials (number of patients seen to arrive at the observed figure), the required probability of success (the expected probability of development of trilateral retinoblastoma as derived from other published reports9), and the logical value associated with the function (in this case, that the equation is true). The result obtained yields the probability that the observed value is similar to the expected value. The power of the study was calculated using the normal approximation to the binomial test, assuming a statistical significance level of $\alpha = .05$.35 None of the patients described in this report have been included in any other published report on trilateral retinoblastoma.

### RESULTS

There were 214 patients with newly diagnosed retinoblastoma during the 54-month study period. Of this group, 142 patients were treated using the chemoreduction protocol of Wills Eye Hospital and The Children's Hospital of Philadelphia11 plus focal adjuvant methods. During the same period, 72 children were treated with nonchemoreduction methods. All patients had routine magnetic resonance imaging or computed tomography of the central nervous system on an annual or biannual basis until aged 4 or 5 years to screen for intracranial malignancy.

#### CHEMOREDUCTION GROUP

In the 142 patients in the chemoreduction group, the mean patient age was 14 months (median, 8 months; range, 1-87 months). Of these, 108 (76%) were white; 22 (15%), African American; 9 (6%), Hispanic; and 3 (2%), Asians. Eighty-one (57%) were boys and 61 (43%) were girls. The tumors were unilateral in 47 (33%) and bilateral in 95 (67%), and the disease was sporadic in 111 (78%) and familial in 31 (22%). Of the 31 familial cases, 27 were bilateral and 4 were unilateral, with 1 previous generation affected with retinoblastoma in 20 cases and 2 previous generations affected in 9.

Chemoreduction was administered for a mean of 5 cycles (median, 2; range, 1-8). The mean age at date last seen was 47 months (median, 44 months; range, 8-134 months). There were no cases of intracranial neuroblastic malignancy detected in this group of children during the mean follow-up of 34 months (median, 32 months; range, 0-67 months) (Table).

In the chemoreduction group, 99 children were at risk for an intracranial tumor, 93 with bilateral retinoblastoma and 4 with unilateral familial disease. Based on a recently published meta-analysis of hereditary retinoblastoma associated with intracranial neuroblastic tumor,4 one would have expected 5 to 15 (5%-15%) of the 99

### Table

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Chemoreduction</th>
<th>Nonchemoreduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At-Risk Patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>199</td>
<td>18</td>
</tr>
<tr>
<td>Expected, No. (%)*</td>
<td>5-15 (5-15)</td>
<td>1-3 (5-15)</td>
</tr>
<tr>
<td>Observed, No. (%)†</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td><strong>Patients With Unilateral Sporadic Retinoblastoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>43</td>
<td>54</td>
</tr>
<tr>
<td>Expected, No. (%)*</td>
<td>&lt;1 (0.05)</td>
<td>&lt;1 (0.05)</td>
</tr>
<tr>
<td>Observed, No. (%)†</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>All Patients With Retinoblastoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>142</td>
<td>72</td>
</tr>
<tr>
<td>Expected, No. (%)*</td>
<td>4 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Observed, No. (%)†</td>
<td>0</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Expected number of patients with trilateral retinoblastoma on the basis of published meta-analysis from Kivela.4
†Observed number of patients with trilateral retinoblastoma in our data.
The association of intraocular retinoblastoma with intracranial malignancy was initially recognized in 1977. In 1994, the clinical variations and outcomes were reported in 13 consecutive patients with trilateral retinoblastoma. The often fatal intracranial neuroblastic malignancy (trilateral retinoblastoma) developed in 13 (3%) of 440 consecutive children with retinoblastoma and 11 (5%) of 202 children with bilateral retinoblastoma. Subsequently, a comprehensive meta-analysis of all published reports of trilateral retinoblastoma has been provided, and the author concluded that routine screening by means of neuroimaging could improve the cure rate, especially if the intracranial tumor was detected at a size smaller than 15 mm. In addition, most cases of trilateral retinoblastoma can be detected within 1 year of the diagnosis of retinoblastoma or even concurrently, if routine screening with brain imaging is performed. It has been our policy during the past decade to advise annual or biannual neuroimaging in children with bilateral or familial retinoblastoma.

Since the time of the initial reports on trilateral retinoblastoma, management of intraocular retinoblastoma has evolved from an exclusive reliance on surgery and radiotherapy to the use of chemotherapy coupled with local measures. Most children with bilateral or familial retinoblastoma are now treated with initial chemoreduction, which has been shown to reduce tumors to a size suitable for treatment with focal adjuvant measures, thereby avoiding external beam radiotherapy. Several such protocols exist, and they all include agents that have been found to be effective for the treatment of primitive neuroectodermal neoplasms of the central nervous system in children. During the past 6 years, we have used a consistent 3-agent regimen of carboplatin, vincristine, and etoposide administered generally for 6 cycles. Minor exceptions to this protocol have occurred with those who display chemotherapy intolerance, local tumor recurrence, or personal preferences. We have found satisfactory tumor control when chemoreduction is coupled with local tumor treatment using thermotherapy or cryotherapy, but recurrence of subretinal and vitreous seeds can be problematic. The systemic toxic effects of this chemotherapy regimen are usually tolerable, and a review of 47 children revealed mild and transient cytopenias (83%), fever (28%), infection (9%), and nonspecific gastrointestinal tract symptoms with dehydration and/or vincristine neurotoxic effects (40%). Renal toxic or ototoxic effects or second malignancy was not detected in any patient.

In this study, we present data on 142 children with retinoblastoma treated with carboplatin, vincristine, and etoposide for a median of 6 cycles. Ninety-nine of these 142 children had bilateral and/or familial disease. Based on the published meta-analysis regarding trilateral retinoblastoma, one would have expected 5% to 15% or 1 to 3 of the 18 children to have developed intracranial neuroblastic tumor. At a mean age of older than 4 years at last follow-up, intracranial tumor developed in 1 patient, consistent with the expected frequency (Table). This patient had second-generation bilateral familial retinoblastoma, and the intraocular tumors were treated successfully using cryotherapy and laser photocoagulation, avoiding chemoreduction and radiotherapy. The pinealoblastoma was diagnosed 26 months after initial diagnosis of retinoblastoma, and the patient died 19 months later.

**NONCHEMOREDUCTION GROUP**

In the 72 patients in the nonchemoreduction group, the mean patient age was 24 months (median, 22 months; range, 1-101 months). Of these, 58 (81%) were white; 6 (8%), African American; 4 (6%), Hispanic; and 4 (6%), Asian. Thirty-one (43%) were boys; 41 (57%), girls. The tumors were unilateral in 55 (76%) and bilateral in 17 (24%), and the disease was sporadic in 65 (90%) and familial in 7 (10%). Of the 7 familial cases, 6 cases were bilateral and 1 case was unilateral, with 1 previous generation affected with retinoblastoma in 5 familial cases and 2 previous generations affected in 2.

The mean age at date last seen was 54 months (median, 52 months; range, 9-120 months). During the mean follow-up of 30 months (median, 31 months; range, 5-58 months), 1 case of an intracranial neuroblastic malignant neoplasm was detected.

Eighteen patients were at risk for trilateral retinoblastoma, 17 patients with bilateral retinoblastoma and 1 patient with unilateral familial disease. Based on the recently published meta-analysis regarding trilateral retinoblastoma, one would have expected 5% to 15% or 1 to 3 of the 18 children to have demonstrated intracranial neuroblastic tumor. At a mean age of older than 4 years at last follow-up, intracranial tumor developed in 1 patient, consistent with the expected frequency (Table). This patient had second-generation bilateral familial retinoblastoma, and the intraocular tumors were treated successfully using cryotherapy and laser photocoagulation, avoiding chemoreduction and radiotherapy. The pinealoblastoma was diagnosed 26 months after initial diagnosis of retinoblastoma, and the patient died 19 months later.
It is not yet known whether this approach will prevent or simply delay the development of trilateral retinoblastoma. However, we speculate that if the immature intracranial precursor cells responsible for this neoplasm have a longer opportunity to mature and are prevented from undergoing the additional steps necessary for malignant transformation, we can expect fewer tumors to develop. Longer follow-up will be necessary to further evaluate the full effect of chemoreduction on trilateral retinoblastoma. There is also the possibility that resistance to these drugs will develop before complete maturation of precursor cells.

CONCLUSIONS

Trilateral retinoblastoma is a highly fatal condition. We have observed strikingly fewer-than-expected numbers of trilateral retinoblastoma in children who were treated with a regimen of carboplatin, vincristine, and etoposide. These agents may have protected children with retinoblastoma from development of this tumor. Chemotherapy in these children could have some unexpected delayed effects that require longer follow-up to identify. However, the chemoreduction method in children with bilateral or familial retinoblastoma appears to be beneficial for management of the intraocular tumors and possibly for prevention or delay of the associated intracranial neoplasm.

Accepted for publication March 30, 2001.

Support provided by the Paul Kayser International Award of Merit in Retina Research, Houston, Tex (Dr J. Shields); the Macula Foundation, New York, NY (Dr C. Shields); and the Eye Tumor Research Foundation, Philadelphia (Dr C. Shields).

Presented by Dr C. Shields as a poster at the American Academy of Ophthalmology in Dallas, Tex, October 24-25, 2000; and at the Association for Research in Vision and Ophthalmology, Ft Lauderdale, Fla, April 31, 2001.

Corresponding author and reprints: Carol L. Shields, MD, Ocular Oncology Service, Wills Eye Hospital, 900 Walnut St, Philadelphia, PA 19107 (e-mail: carol.shields@shieldsoncology.com).

REFERENCES