Ocular Motility Changes After Subtenon Carboplatin Chemotherapy for Retinoblastoma

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Background: Focal subtenon carboplatin injections have recently been used as a presumably toxicity-free adjunct to systemic chemotherapy for intraocular retinoblastoma.

Objective: To report our clinical experience with abnormal ocular motility in patients treated with subtenon carboplatin chemotherapy.

Methods: We noted abnormal ocular motility in 10 consecutive patients with retinoblastoma who had received subtenon carboplatin. During ocular manipulation under general anesthesia, we assessed their eyes by forcedduction testing, comparing ocular motility after tumor control with ocular motility at diagnosis. Eyes subsequently enucleated because of treatment failure (n=4) were examined histologically.

Results: Limitation of ocular motility was detected in all 12 eyes of 10 patients treated for intraocular retinoblastoma with 1 to 6 injections of subtenon carboplatin as part of multimodality therapy. Histopathological examination revealed many lipophages in the periorbital fat surrounding the optic nerve in 1 eye, indicative of phagocytosis of previously existing fat cells and suggesting prior fat necrosis. The enucleations were technically difficult and hazardous for globe rupture because of extensive orbital soft tissue adhesions.

Conclusions: Subtenon carboplatin chemotherapy is associated with significant fibrosis of orbital soft tissues, leading to mechanical restriction of eye movements and making subsequent enucleation difficult. Subtenon carboplatin is not free of toxicity, and its use is best restricted to specific indications.

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Retinoblastoma (RB), the most common intraocular malignancy of childhood, occurs in approximately 1 in 20000 live births. Most of the cases are in children younger than 2 years, with tumors arising from primitive retinal cells. The tumors of patients with bilateral RB may be multifocal or unifocal, and involvement is usually more extensive in 1 eye. The tumors of patients with unilateral RB may also be multifocal. In recent years, new regimens have shown considerable success in treating intraocular RB using multiagent chemotherapy—with or without cyclosporine to address the problem of multidrug resistance P-glycoprotein that is associated with RB tumors—combined, in most cases, with local laser therapy and cryotherapy to consolidate the response to chemotherapy. These regimens often use systemic carboplatin, etoposide, and vincristine sulfate (CEV) and, recently, subtenon injections of carboplatin as adjunctive local therapy. The rationale for using subtenon injections is to increase the intraocular concentration of carboplatin, without incurring additional systemic toxicity from increasing intravenous carboplatin dosages. We report our clinical observation of decreased ocular motility associated with subtenon carboplatin in our patients.

METHODS

Our main indications for subtenon carboplatin adjunctive therapy were preservation of (1) the remaining eye in patients with bilateral poor-prognosis RB who already had 1 eye enucleated, (2) both eyes in patients with bilateral RB having poor-prognosis tumors at diagnosis, or (3) eyes in patients in whom systemic chemotherapy was contraindicated. Ten consecutive children with newly diagnosed retinoblastoma who received local subtenon carboplatin (9 concurrently receiving systemic CEV and cyclosporine chemotherapy) at The Hospital for Sick Children between January 1, 1999, and December 31, 2001, were noted to have abnormal ocular motility. We assessed ocular motility by forcedduction testing as part of the routine clinical examination under anesthesia at the time of ocular manipulation for any patient receiving sub-
Ocular Outcomes From Subtenon Carboplatin Injections and Systemic Carboplatin, Etoposide, and Vincristine Sulfate (CEV) Chemotherapy

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, mo</th>
<th>No. of Systemic CEV Cycles</th>
<th>Eye</th>
<th>No. of Injections</th>
<th>Location</th>
<th>Grade/Restriction of Traction Testing</th>
<th>Tumor Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/162</td>
<td>0</td>
<td>OD</td>
<td>0 (Normal eye)</td>
<td>Inferior quadrants</td>
<td>2/Elevation</td>
<td>No active tumor</td>
</tr>
<tr>
<td>2/F/22</td>
<td>8*</td>
<td>OD</td>
<td>3</td>
<td>Inferior quadrants</td>
<td>3/Elevation; 2/depression; enophthalmos</td>
<td>Enucleated</td>
</tr>
<tr>
<td>3/F/6</td>
<td>4*</td>
<td>OD</td>
<td>0 (Already enucleated)</td>
<td>Inferior quadrants</td>
<td>2/Elevation; 1/all directions</td>
<td>No active tumor</td>
</tr>
<tr>
<td>4/F/7</td>
<td>8†</td>
<td>OD</td>
<td>6</td>
<td>Inferior quadrants</td>
<td>3-4/All directions; enophthalmos</td>
<td>No active tumor</td>
</tr>
<tr>
<td>5/M/19</td>
<td>7*</td>
<td>OD</td>
<td>4</td>
<td>Inferior quadrants</td>
<td>2/Elevation</td>
<td>Enucleated</td>
</tr>
<tr>
<td>6/M/16</td>
<td>6*</td>
<td>OD</td>
<td>0 (Normal eye)</td>
<td>Inferior quadrants</td>
<td>1/Elevation</td>
<td>Enucleated</td>
</tr>
<tr>
<td>7/F/3</td>
<td>7*</td>
<td>OD</td>
<td>0 (Controlled by CEV)</td>
<td>Inferior quadrants</td>
<td>3/All directions; enophthalmos</td>
<td>No active tumor</td>
</tr>
<tr>
<td>8/M/12</td>
<td>10†</td>
<td>OD</td>
<td>3</td>
<td>Inferior quadrants</td>
<td>2/Elevation and depression</td>
<td>No active tumor</td>
</tr>
<tr>
<td>9/M/9</td>
<td>4*</td>
<td>OD</td>
<td>0 (Already enucleated)</td>
<td>Inferior and superior quadrants</td>
<td>1/Elevation</td>
<td>No active tumor</td>
</tr>
<tr>
<td>10/F/25</td>
<td>7*</td>
<td>OD</td>
<td>1</td>
<td>Inferior quadrants</td>
<td>3/Elevation</td>
<td>Enucleated</td>
</tr>
</tbody>
</table>

*Cyclosporine (33 mg/kg) was given over 3 hours on each of the 2-day chemotherapy cycles, in which carboplatin (28 mg/kg) was given on day 1 and vincristine sulfate (0.05 mg/kg) and etoposide (12 mg/kg) were given on day 2.
†Carboplatin (22 mg/kg), etoposide (9 mg/kg), and vincristine sulfate (0.05 mg/kg) and cyclosporine (33 mg/kg) were given on each of the 2-day chemotherapy cycles. Patient 8 received 7 cycles of chemotherapy at the higher dosages and 3 cycles of chemotherapy at the lower doses.

RESULTS

Twelve eyes of 10 patients with RB were treated with 36 subtenon carboplatin injections. The median age at diagnosis was 12 months (range, 3 months to 13½ years). All children were seen by 25 months of age except for patient 1, who was seen at age 13½ with retinoblastoma reactivation in a unilateral retina.

Seven children had bilateral tumors and 3 had unilateral tumors. Of the 7 children with bilateral RB, 2 required subtenon carboplatin injections in 1 eye only because tumors in their other eye had been controlled by systemic CEV and cyclosporine and local laser therapy, 3 had their other eye already enucleated at diagnosis, and 2 were treated with subtenon carboplatin in both severely involved eyes. Nine patients received a mean of 7 cycles of systemic CEV and cyclosporine.

The mean number of subtenon injections was 3 per eye at 3- to 4-week intervals. All parents reported some periorcular swelling and redness for several days after injection that resolved spontaneously.

Forced duction testing revealed restriction of ocular rotation after subtenon carboplatin injections in all 12 treated eyes (Table), with the direction of restriction correlating with the sites of injections. Restriction of eye movements was detected after as few as 1 subtenon carboplatin injection and as early as the next examination under anesthesia 3 to 4 weeks later. Patient 1, for example, received 4 subtenon carboplatin injections in the inferior quadrants of the left eye and developed a grade 2 limitation of elevation of the eye (Figure 1). Attempted forced elevation showed marked restriction of movements of the left eye, in contrast to normal movements of the un.injected right eye (Figure 2A and B). Two eyes with multiple injection sites (right eye of patient 4 and left eye of...
patient 7) had restriction of ocular rotation in all directions and a significant enophthalmos. The degree of motility restriction was generally greater with an increased number of subtenon carboplatin injections. Figure 3 shows the correlation ($r=0.8$) of the mean grade of the degree of restriction of ocular movement with the number of subtenon carboplatin injections. No mechanical restriction of ocular rotation has been detected in the eyes of patients treated only with laser therapy and cryotherapy without local carboplatin.

Four eyes required enucleation for uncontrolled tumor growth 2 to 4 months following their most recent subtenon carboplatin injection (Table). These 4 eyes had been treated with systemic chemotherapy, laser therapy, and cryotherapy, but had received no irradiation. Forced duction testing in patient 2 before enucleation revealed a marked grade 3 restriction of elevation and moderate grade 2 limitation of depression in both eyes, which had been treated with subtenon carboplatin. At enucleation, extensive conjunctival scarring was noted in all 4 cases, making the surgery difficult and hazardous for potential rupture of the globe. In patient 2, the orbital fat attached to the globe appeared opaque white and abnormal (Figure 4A). There was viable intraocular RB within the enucleated eye, but no evidence of extraocular extension. Microscopic examination of this eye showed many lipophages in the periorbital fat surrounding the optic nerve, indicative of phagocytosis of previously existing fat cells and, in this context, was suggestive of prior fat necrosis (Figure 4B). Fibrosis also made surgery difficult in the other 3 enucleations, but orbital fat necrosis was not noted. These tumors had not extended into the optic nerves.

Adequate tumor control was achieved in 8 (67%) of 12 eyes that were retained (Table). In addition to en-
ophthalmos and restriction of ocular motility, there was a variable foreshortening of the conjunctival fornices in all treated eyes, making indentation for examination and focal treatment of the peripheral retina difficult. Furthermore, satisfactory fitting of the prosthesis following enucleation was difficult because of shrinkage of the conjunctival fornices and considerable loss of orbital soft tissue volume.

COMMENT

Enucleation of the worse eye and irradiation of the better eye has been the traditional treatment for bilateral advanced RB for the past 30 years. External beam radiation, although effectively controlling many intraocular tumors, is associated with severe long-term complications, including second malignancies, cataracts, cosmetic deformity of the orbit, lacrimal dysfunction, radiation retinopathy, and, rarely, growth hormone deficiency. For this reason, we use chemotherapy when there is no indication at diagnosis for immediate enucleation of 1 or both severely involved eyes in patients with bilateral RB (ie, no suspicion of extraocular extension, anterior segment involvement, neovascular glaucoma, or orbital cellulitis). Chemotherapy has not been associated with the severe long-term adverse effects that complicate radiotherapy. We use a combination of chemotherapy and local therapy as the primary treatment. Our protocol includes CEV chemotherapy with cyclosporine as primary therapy. We use cyclosporine to address the problem of multidrug resistance P-glycoprotein that frequently besets RB tumors. We use local laser therapy and cryotherapy for consolidation after tumor shrinkage from chemotherapy. These local modalities are only effective for small tumors less than 2 mm in height and for some medium tumors of 2 to 4 mm in height.

When first described in a mouse model, and in treatment of human RB tumors, subtenon carboplatin was viewed as a useful, toxicity-free local therapy. In the mouse model, no histopathological toxicity was detected 11 weeks after subtenon carboplatin injections. The initial study by Abramson et al reported painless periorbital edema and redness after injection in 4 of 13 eyes treated, which subsided after several days. No long-term adverse effects were reported except for an inexplicable case of optic neuropathy. The effect of carboplatin on periorbital tissues was not examined, and no comment was made on its potential effect on ocular motility. Because of anecdotal results, subtenon carboplatin was considered harmless, and it has been widely used, particularly for patients in whom other therapies failed to achieve tumor control. We have used this adjunctive therapy in combination with systemic chemotherapy and focal therapy for poor-prognosis intraocular RB in both eyes or in the remaining eye after enucleation of 1 eye, or when systemic chemotherapy was contraindicated.

Figure 3. Plot showing the correlation (\(r = 0.8\)) between the mean grade of the degree of restriction of ocular movements in the 12 treated eyes and the number of subtenon carboplatin injections. Grade 0 indicates no limitation; 4, no movement beyond the primary position.

Figure 4. Fat necrosis after subtenon carboplatin injection in the right eye of patient 2. A, Gross specimen enucleated 8 weeks after the last of 3 subtenon carboplatin injections shows atrophic orbital fat, appearing opaque white and abnormal (arrows). B, Periorbital fat shows normal fat (black arrow), surrounded by several lipophages (white arrow) (hematoxylin-eosin, original magnification \( \times 100 \)).
The use of systemic chemotherapy for malignancies has been associated with ocular toxicities. For instance, cranial nerve paralysis is an uncommon complication of vincristine therapy, and maculopathy, optic neuritis, uveal effusion, cortical blindness, and orbital inflammation are rare complications of systemic carboplatin therapy. Lauer et al reported an unusual case of uveal effusion, angle closure glaucoma, orbital inflammation, external ophthalmoplegia, and residual ocular motility disturbance that complicated the use of intracarotid carboplatin and etoposide therapy for a brain tumor. However, such rare ocular toxicities have not been observed in our long-term cohort of 60 patients treated since 1991 with 2 consecutive CEV and cyclosporine protocols.

Using the same dosage and concentration of carboplatin used by Abramson et al, we observed previously unreported ocular toxicity in the form of restriction of ocular movements in all patients. All of our patients developed periorbital swelling following each carboplatin injection; therefore, this drug may be the cause of an orbital inflammatory reaction secondary to fat necrosis. Subsequent healing with fibrosis may account for the restriction of ocular motility and enophthalmos. Furthermore, the scarring of the orbital tissues rendered subsequent enucleations hazardous for potential spill of therapy-resistant tumor. Therefore, this local therapy for RB that was considered innocuous is associated with previously unidentified and unreported significant cosmetic and functional complications.

We cannot comment on the efficacy of local carboplatin, because we have not studied this therapy in isolation from systemic chemotherapy. However, it is our impression that a reduction in tumor size correlates with the administration of subtenon carboplatin, particularly for small-volume tumors. The potential risk-benefit of combining local carboplatin therapy with systemic chemotherapy and local laser or cryotherapy must be considered in planning the treatment of individual patients with RB. We use local carboplatin therapy only for specific indications, and we limit the number of doses to 4.

The most serious complication is periorbital scarring, making subsequent enucleation at risk for rupture of the globe and dissemination of resistant tumor. These adverse effects of subtenon carboplatin injections should be disclosed to parents as part of the informed consent of potential risk-benefit in the management of RB.

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REFERENCES