Globe-sparing interventions in the management of intraocular retinoblastoma

RETINOBLASTOMA is the most common malignant intraocular tumor in children; it is also one of the most highly curable pediatric solid tumors if detected early. The conventional treatment of retinoblastoma is primary enucleation. Recent research reported a trend toward decreasing frequency of enucleation in the management of retinoblastoma. The trend toward globe-sparing interventions has been largely attributed to earlier diagnosis and recent success with conservative globe-sparing treatment options. Currently, globe-sparing interventions include first-line chemotherapy or chemoreduction, subconjunctival chemotherapy, systemic chemotherapy for metastasis, transpupillary thermotherapy (TTT), chemothermotherapy (CTT), laser photocoagulation, cryotherapy, brachytherapy, and external beam radiotherapy (EBRT). Expanded clinical options currently available have markedly decreased the overall enucleation rate for retinoblastoma.

CLINICAL SCENARIO

A 10-month old boy is brought to an ophthalmologist because of cat's eye reflex in the left eye. The patient had undergone enucleation of his right eye for glaucomatous stage retinoblastoma 6 months earlier. Examination revealed the presence of a solitary retinal mass of about 12 mm in diameter, located nasal to the disc. There was no evidence of vitreous seeding.

Realizing that this was the only eye of the patient, the ophthalmologist wants to do everything humanly possible to preserve it. He has heard about chemothermotherapy (CTT) but is not sure if this was the best alternative he can offer.

CLINICAL QUESTION

Among patients with retinoblastoma, is chemoreduction combined with adjuvant treatment effective in preserving the globe and vision?
SEARCH METHOD
An electronic search of the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) on The Cochrane Library (Issue 1 2005) and MEDLINE on PubMed was performed. The literature search was limited to the English language with no date restrictions. The search terms used were retinoblastoma and chemothermo-therapy, thermochemotherapy, or chemoreduction. The search yielded 70 articles, 22 were chosen for evaluation and 8 were included in the review. Two reviewers independently assessed the articles for inclusion.

Selection criteria
This review was designed to include clinical trials in which treatment of retinoblastoma with chemoreduction combined with adjuvant therapy was compared with another treatment or no treatment.

CITATIONS

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Method</th>
<th>Ocular preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schiavetti, et al. J Pediatr Hematol Oncol 2005</td>
<td>58 eyes, 46 patients</td>
<td>Chemoreduction (carboplatin/ etoposide)* Adjuvant treatment (laser or cryo)</td>
<td>Tumor response rate</td>
<td>Prospective, nonrandomized clinical trial</td>
<td>67%</td>
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<tr>
<td>Shields, et al. Am J Ophthalmol 2004</td>
<td>457 tumors (193 eyes, 125 patients)</td>
<td>Chemoreduction (vincristine, etoposide, carboplatin) * Adjuvant treatment (cryo, thermo, or both)</td>
<td>Tumor recurrence</td>
<td>Prospective, single-center, interventional case series</td>
<td>98% (22%**)</td>
</tr>
<tr>
<td>Schueler, et al. Br J Ophthalmal 2003</td>
<td>55 tumors (28 patients with bilateral RB)</td>
<td>Chemothermotherapy (CTT)</td>
<td>Tumor recurrence</td>
<td>Prospective, nonrandomized clinical trial</td>
<td>96% (38%**)</td>
</tr>
<tr>
<td>Shields, et al. Arch Ophthalmal 2002</td>
<td>30 patients with unilateral RB</td>
<td>Chemoreduction plus focal treatment (cryo, thermo, plaque)</td>
<td>Need for EBR or enucleation</td>
<td>Prospective, nonrandomized single-center clinical trial</td>
<td>71% (33%*)</td>
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<tr>
<td>Wilson, et al. Ophthalmology 2001</td>
<td>36 eyes</td>
<td>Chemotherapy (carboplatin &amp; vincristine) (local treatment given only when disease progressed)</td>
<td>Disease progression, delay of EBR, ocular survival</td>
<td>Noncomparative, prospective case series</td>
<td>19.50%</td>
</tr>
<tr>
<td>Shields, et al. Ophthalmology 1997</td>
<td>130 tumors (52 eyes, 32 patients)</td>
<td>Chemoreduction (vincristine, etoposide, carboplatin) + Adjuvant treatment (cryo, laser, thermo, CTT, plaque, EBR)</td>
<td>Tumor control</td>
<td>Prospective, nonrandomized clinical trial</td>
<td>58%</td>
</tr>
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</table>

* Reese–Ellsworth V   cryo – cryotherapy
** Tumor-recurrence rate   thermo – thermotherapy
EBR – external beam radiotherapy
RB – retinoblastoma

**DISCUSSION**

Data collection and analysis

No randomized controlled clinical trials were found. The available literature consists mostly of prospective nonrandomized clinical trials and interventional case series (Level 4 evidence). The reviewers extracted data and assessed trial quality of the included studies. Due to the variability in treatment methods and main outcome measures, no statistical summary measure was calculated.

Main results

Eight trials were included in this review (Table 1). The highest rate of globe preservation (98%) was shown in a study of 193 eyes in 125 children (457 tumors) treated with chemotherapy plus adjuvant therapy, consisting of either cryotherapy or transpupillary thermotherapy or both. In this study, the rate of recurrence leading to subsequent enucleation or external beam radiation rose with greater tumor thickness and when the tumors were at the macula. Two other trials on chemothermotherapy (CTT), which consisted of intravenous (IV) administration of carboplatin followed shortly by transpupillary thermotherapy (TTT), yielded globe-salvage rates of 92% to 96%. This intervention was particularly effective in small to medium tumors (up to 12 mm). Globe-preservation rates were much lower (58%-67%) when chemoreduction was combined with other modes of adjuvant or focal treatments (cryotherapy, laser therapy, plaque radiotherapy). Chemotherapy alone posted the lowest globe-preservation rate of 19.5%. In most trials, globe-preservation rates were much lower for tumors classified as Reese–Ellsworth (RE) V. Two trials studied the factors that led to treatment with enucleation or external beam radiation. Results were not consistent.

**STUDY AUTHORS’ CONCLUSIONS**

Classifications of retinoblastoma based on disease severity have been developed to aid in the prediction of globe salvage. The Reese–Ellsworth classification, which correlates the likelihood of globe salvage with tumor extent, is widely used in most research studies (Table 2).

The available treatment methods for retinoblastoma for globe salvage in the management of retinoblastoma include intravenous chemoreduction, thermodermotherapy, cryotherapy, laser photocoagulation, plaque radiotherapy, external beam radiotherapy, and systemic chemotherapy for metastatic disease.3

Chemoreduction with or without adjunctive focal measures and thermotherapy alone have been the most promising of the globe-sparing modalities described.

**Chemoreduction**

Chemoreduction is a method of reducing tumor volume by means of chemotherapeutic agents. This allows the use of adjunctive therapeutic measures that are more focused and less damaging, increasing the likelihood of globe salvage. The chemotherapeutic agents employed are varied and depend on the preference of the pediatric oncologist, but consist mainly of a combination of the following agents: carboplatin, etoposide, and vincristine. The chemotherapy regimen is generally given in 6 cycles for adequate tumor reduction. Adjunctive focal therapy if given is delivered at cycle 2 after achieving adequate tumor reduction. Chemoreduction allows for a reduction in tumor size that permits focal treatments to be applied to a smaller area, preserving more vision and delaying or possibly avoiding enucleation.4


Although all groups of patients with intraocular retinoblastoma responded to carboplatin/etoposide chemotherapy associated with focal therapy, all the cases in RE group V relapsed. This approach is questionable in RE group V, where delaying aggressive treatment in a very young child may be justified.


Chemoreduction alone or combined with cryotherapy or thermotherapy is effective for treatment of retinoblastoma, but tumor recurrence rate is highest when

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### Table 2. Reese–Ellsworth (RE) classification for conservative treatment of retinoblastoma.*

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<tr>
<th>Group</th>
<th>Likelihood of Globe Salvage</th>
<th>Features</th>
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| I     | Very favorable               | • Solitary tumor, less than 4 disc diameters, at or behind equator  
|       |                              | • Multiple tumors, none over 4 disc diameters, all at or behind equator |
| II    | Favorable                    | • Solitary tumor, 4 to 10 disc diameters, at or behind equator  
|       |                              | • Multiple tumors, 4 to 10 disc diameters, behind equator |
| III   | Doubtful                     | • Any lesion anterior to equator  
|       |                              | • Solitary tumors larger than 10 disc diameters behind equator |
| IV    | Unfavorable                  | • Multiple tumors, some larger than 10 disc diameters  
|       |                              | • Any lesion extending anteriorly to ora serrata |
| V     | Very unfavorable             | • Massive tumors involving more than half of retina  
|       |                              | • Vitreous seeding |

*Refers to chances of salvaging the affected eye and not systemic prognosis.
the tumor is thicker (risk ratio of 1.13 per 1 mm increase) or located in the macula (risk ratio 3.58).

Chemoreduction offers satisfactory retinoblastoma control for RE groups I-IV, with treatment failure necessitating additional external beam radiotherapy in only 10% of eyes and enucleation in 15% of eyes at five-year follow-up. RE group V requires external beam radiotherapy in 47% and enucleation in 53% at 5 years.

Chemoreduction is an option for selected eyes with unilateral retinoblastoma. Those with advanced RE group V retinoblastoma showed poorest results, while those with less advanced groups I through IV disease showed best results, maintaining the globe in 71% of eyes, occasionally with satisfactory functional visual acuity.

Multiagent chemotherapy alone does not ensure a cure for multifocal intraocular retinoblastoma. Supplemental focal therapy is needed to control disease progression.

Chemoreduction and adjutant treatment of intraocular retinoblastoma with seeding provide good retinal tumor control, even in eyes with advanced disease. Chemoreduction alone generally is not adequate to achieve complete tumor seed control. Cautious follow-up of affected patients is recommended because the risk for recurrent vitreous and subretinal seeds is substantial and proper treatment is critical for salvaging the eye.

Thermochemotherapy
Therapy is a focal or adjunctive treatment modality that applies focused heat to tissue at subphotocoagulation levels to induce tumor necrosis in the treatment of intraocular masses. A transpupillary diode-laser system is used to selectively increase temperature in the tumor. The goal is to attain a focal temperature rise of 42° to 60° Celsius, which is below the coagulative threshold sparing the surrounding retinal tissues. The thermal action has been found to have a synergistic effect by increasing the cytotoxic effects of platinum analogues in the treatment of retinoblastoma. The combination of heat and chemotherapy is called chemothermotherapy (CTT).

Chemothermotherapy using an indirect laser ophthalmoscope with a spot size of about 400 µm was efficient for retinoblastoma with a tumor height less than 4 mm. In larger tumors, the recurrence rate was unacceptably high (risk ratio 1.36). Fish flesh regression after TCT correlates with a higher rate of local tumor recurrence (risk ratio 4.88). Treatment-related complications occurred in less than 9% of the treated eyes.

Chemothermotherapy is an effective technique to treat small- to medium-sized retinoblastomas in children, avoiding external beam irradiation.

REVIEWERS’ CONCLUSIONS
The evidence as to the effectiveness of chemoreduction combined with adjuvant or focal therapy comes mainly from nonrandomized, interventional case series (Level 4 evidence). There is evidence that chemothermotherapy provides the best chance for ocular (globe) preservation. Chemoreduction combined with other forms of adjuvant or focal therapy showed poorer outcomes compared with CTT, but is still better than chemotherapy alone. There is no evidence that chemoreduction with adjuvant therapy leads to preservation of vision. If at all possible, further large well-conducted randomized controlled trials, with longer follow-up, are advisable.

RESOLUTION OF THE CLINICAL SCENARIO
For intraocular tumors ≤10 mm, with no evidence of vitreous and/or retinal seeding (RE I-IV), chemothermotherapy offers the best chance for globe preservation (Grade C recommendation).

References