keratoconus. The published cases that developed haze either had stage III keratoconus or more advanced changes including thinner corneas, higher keratometry values, and prominent Vogt striae. Mazzotta et al. reported that hyporeflective bands in a reticular pattern representing stromal microstriae prior to CXL could be a confocal sign of advanced keratoconus, predicting haze formation. This pattern was not seen in our cases, consistent with the milder clinical picture. Despite the lower risk profile of our patients, both developed dense, deep stromal scars that were morphologically different and more severe than the faint haze described by Mazzotta et al. and Raiskup et al. The deep stromal scar also occurred at the junction between the treated and untreated cornea along the demarcation line, which has not been previously described. Mazzotta et al. also described increased keratocyte density in the region of the scar, in contrast to the reduced keratocyte population in our cases. Riboflavin–UV-A exposure typically causes keratocyte apoptosis in the early postoperative period, and we speculate that a sublethal effect in the deep stroma where the UV-A irradiation dose is lower may lead instead to fibroblastic transformation and an aberrant scarring response. This would explain the delayed reaction seen and, if proven in subsequent study, may suggest that longer or higher-intensity UV-A irradiation is indicated. Performing a modification of the technique in which the epithelium is not removed may also help prevent this complication.

In conclusion, deep corneal stromal scar formation may complicate CXL for mild keratoconus and, if severe, may lead to a significant increase in astigmatism.

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Multifaceted Chemotherapy for Trilateral Retinoblastoma

Trilateral retinoblastoma (TRB) occurs in 3% of patients with unilateral or bilateral germline retinoblastoma. This midline malignant neuroectodermal tumor arises commonly in the pineal gland (77%-83% of patients) and less frequently in the paraspinal region (17%-23% of patients). Trilateral retinoblastoma is difficult to treat and usually fatal. Complete resection is seldom possible for tumors in the pineal or paraspinal locations. Craniospinal irradiation is too damaging to the growth, intellectual, cognitive, and endocrine functions, particularly for children younger than 3 years of age. Chemotherapy alone rarely cures young children with other intracranial neuroectodermal tumors, such as medulloblastoma. Trilateral retinoblastoma often presents with dissemination in the cerebrospinal fluid (CSF) (leptomeningeal TRB or neoplastic meningitis) and is extremely difficult to cure because most intra- thecal drugs are ineffective for solid-tumor CSF metastases.

We designed a multifaceted chemotherapy regimen for TRB. For induction, we used our Toronto Protocol, which consists of high-dose cyclosporine A (CSA), an inhibitor of the multidrug resistance P-glycoprotein (p170), to modulate a high dose of carboplatin, etoposide, and vincristine sulfate (hereafter referred to as CEV), which is described in Chan et al. for treatment of children with intraocular retinoblastoma. Intraventricular to- potecan hydrochloride combined with cytarabine was given via an Ommaya reservoir, and this method of treatment was previously shown to be effective for treating CSF metastases. To avoid craniospinal irradiation, we used suprateladalose chemotherapy as consolidation therapy, with rescue of the bone marrow by autologous peripheral stem cell transplant. To the best of our knowledge, this multifaceted treatment regimen led to tumor response and to survival beyond that ever reported for a patient with leptomeningeal TRB in any study. The significant extension of survival among the patients reported suggests that this protocol may in some instances offer the potential for cure for leptomeningeal TRB.

Methods. This study reports all cases of TRB from 2000 to 2008 treated at The Hospital for Sick Children (Toronto, Ontario, Canada). All patients were treated during a prospective clinical trial that was approved by the Hospital for Sick Children research ethics board and that conforms to the principles of the Declaration of Helsinki.

Report of Cases. Case 1. A 4-month-old girl had hypothalamic overgrowth syndrome and central blindness from a large suprasellar tumor...
observed on computed tomographic (CT) and magnetic resonance imaging (MRI) scans (Figure, A). Her bilateral retinal tumors were initially diagnosed as astrocytic hamartoma.\textsuperscript{14} Craniopharyngioma or germ cell tumor was suspected, but CSF \textalpha-fetoprotein and \textbeta-human chorionic gonadotropin levels were normal. Needle biopsy of the suprasellar region showed necrotic tumor, but open biopsy confirmed the diagnosis of TRB, with bilateral group B (T1b) eyes, staged according to the International Intraocular Retinoblastoma Classification (IIRC).\textsuperscript{15} Postoperative CSF sample was positive for tumor cells (M1e on TMN staging),\textsuperscript{16} but samples obtained prior to and during the needle biopsy were negative. There were no bone marrow or bone metastases. Her germline \textit{RB1} mutation was a deletion (g.59444 del196) affecting splicing of exon 8.

She responded to 6-cycle systemic CEV-CSA and to intraven-

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**Figure.** Radiological imaging of cases 1, 2, and 3. Case 1 shows a postgadolinium axial T1-weighted magnetic resonance imaging (MRI) scan of a suprasellar tumor at diagnosis (A) (arrow indicates tumor at back of eye) and an axial MRI scan of the same suprasellar tumor before transplant (B). Case 2 shows a postgadolinium axial spectral presaturation with inversion recovery T1-weighted MRI scan of a suprasellar tumor at diagnosis (C) and a postgadolinium axial MRI scan of the same suprasellar tumor before transplant (D). Case 3 shows an axial MRI scan of a suprasellar tumor at diagnosis (E) and an axial MRI scan of the same suprasellar tumor before transplant (F).
tricular cytarabine-topotecan given via an Ommaya reservoir, with clearing of the CSF metastases, shrinkage of the suprasellar (Figure, B) and retinal tumors, and restoration of vision. She received a supralethal dosage of carboplatin, etoposide, and cyclophosphamide as consolidation with autologous peripheral stem cells for bone marrow rescue. However, 19 months after diagnosis and 11 months after transplant, the tumor recurred along the needle biopsy tract, and she died 32 months after the diagnosis was given.

Autopsy revealed multiple subdural and subarachnoid nodular growths and widespread leptomeningeal and ventricular metastases, especially around the needle biopsy tract (data not shown). The suprasellar mass was calcified and nonviable. The eyes showed calcified tumor and retinal scarring, with one tiny focus of viable tumor in the right eye.

Case 2. A 6-month-old boy presented with leukocoria of the left eye, which was classified as IIRC group D (T3a) and enucleated. Two months later, he developed central blindness, and a large suprasellar tumor was found on CT and MRI scans (Figure, C); a small tumor in the right eye was classified as IIRC group A (T1a). He had CSF metastases (M1e stage) but no bone marrow or bone metastases. To avoid risk of tumor dissemination as observed in case 1, the suprasellar tumor was not biopsied. His germline RB1 mutation was a 1-base pair deletion (c.1951delT) in exon 19 causing a premature stop codon and nonfunctional pRB protein.

He responded to 6-cycle systemic CEV-CSA and to intraventricular cytarabine-topotecan, with clearing of CSF metastases, shrinkage of the suprasellar (Figure, D) and retinal tumors, and restoration of vision. He received the autologous peripheral stem cell transplant regimen described for case 1 as consolidation. However, 10 months after diagnosis and 5 months after transplant, the suprasellar tumor recurred, and she died 14 months after diagnosis.

Comment. Our multifaceted chemotherapy regimen, which combines systemic CEV-CSA chemotherapy and intraventricular topotecan-cytarabine for induction and supralethal-dosage chemotherapy consolidation with autologous peripheral stem cell transplant regimen described for case 1 as consolidation. However, 10 months after diagnosis and 5 months after transplant, the suprasellar tumor recurred, and she died 14 months after diagnosis.

Published studies have used 5- to 7-day continuous CSA infusions to reverse tumor-cell p170, but prolonged exposure to CSA also circumvents normal-cell p170. This leads to increased toxicity to p170-expressing bone marrow, liver, kidney, gut, and other tissues and delays liver and renal excretion and metabolism of chemotherapy, thereby further increasing drug exposure to normal tissues.18 We have shown that 3-hour high-dose CSA infusions avoid enhancement of high-dose CEV toxicity (so our patients tolerate chemotherapy well) and are efficacious in modulating retinoblastoma chemotherapy.17

Cytarabine, a pyrimidine antimetabolite antileukemic agent, generally has little anti–solid tumor activity but is not a substrate of p170 and can kill retinoblastoma cell lines in vitro.15 Used together with topotecan (a topoisomerase I inhibitor), which is less susceptible to multidrug resistance, we have successfully cleared CSF metastases, the most difficult type of retinoblastoma metastases to cure.

High-dose craniospinal radiation therapy is not an option for young children because it causes devastating long-term neuro-psychological effects (cognitive and learning problems)19 and hormonal complications (growth, thy-
owing to their germline predisposed to secondary cancers (e.g., leukemia, lymphoma, multiple myeloma, malignant melanoma) in children with TRB who are already predisposed to secondary cancers owing to their germline R1B mutations.

Treatment of TRB using the Toronto Protocol and intrathecal topotecan combined with cytarabine, followed by consolidation with autologous peripheral stem cell transplant after supralethal chemotherapy avoids the need for radiation therapy and, in some instances, extends survival.

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Acute macular neuroretinopathy (AMNR) is a rare retinal condition that features the sudden onset of bilateral central scotomata, which may be preceded by a viral prodrome in some patients. Acute macular neuroretinopathy may be difficult to diagnose because of the subtle or even absent findings on funduscopic examination and fluorescein angiography. Bos and Deutman1 initially described AMNR in 4 patients with paracentral scotomata, slightly decreased visual acuity, and reddish, wedge-shaped intraretinal lesions directed toward the fovea. Because of the acute onset of the symptoms and based on their theory that the more superficial layers of macular retina were involved, the term AMNR was adopted.

Herein, we describe 2 patients with features of AMNR in whom Amsler grid testing, infrared imaging, spectral-domain optical coherence tomography (SD-OCT), fundus autofluorescence, and multifocal electroretinogram (mfERG) were useful in characterizing the precise structural and functional deficits of this condition. The localization of structural deficits to the outer retina and photoreceptor layer using SD-OCT and evidence of depressed cone amplitudes using mfERG in both patients were more consistent with photoreceptor and outer retinal dysfunction. Hughes et al2 previously reported 2 cases of AMNR that featured outer retinal structural changes using SD-OCT. The functional and anatomic deficits observed in our patients using multimodality diagnostic testing, combined with the previous structural characterization of AMNR,2,3 are supportive of the proposed nomenclature acute macular outer retinopathy (AMOR) to more accurately describe this unique clinical entity.2