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 microstraia 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-dose 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 scarring 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 intrathecal 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 cyclophosphamide 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 topotecan 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 suprahathaloid dose 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.14 Cranioopharyngioma or germ cell tumor was suspected, but CSF α-fetoprotein and β-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).15 Postoperative CSF sample was positive for tumor cells (M1e on TMN staging),16 but samples obtained prior to and during the needle biopsy were negative. There were no bone marrow or bone metastases. Her germline RB1 mutation was a deletion (g.59444 del196) affecting splicing of exon 8.

She responded to 6-cycle systemic CEV-CSA and to intraven-
tricular cytarabine-topotecan given via an Ommaya reservoir,14 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,14 with clearing of CSF metastases, shrinkage of the suprasellar (Figure, F) and retinal tumors, and restoration of some vision. She 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 cytarabine-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.

Comment. Our multifaceted chemotherapy regimen, which combines systemic CEV-CSA chemotherapy and intraventricular cytarabine-topotecan 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.
roid, corticosteroid, and sex hormone deficiencies. Radiation therapy greatly increases the lifelong risk of secondary malignant neoplasms (glioblastoma multiforme, malignant astrocytoma, meningioma, bone and soft-tissue sarcoma, and malignant melanoma) in children with TRB who are already predisposed to secondary cancers owing to their germline RBP mutations.

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

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