Treatment of Retinoblastoma in the First 3 Months of Life: Bridge Therapy

BY DAVID H. ABRAMSON, MD, FACS

Treating children with retinoblastoma in the first 3 months of life continues to hold several challenges despite the many advances in retinoblastoma management. This article highlights the reason for these challenges and a new, novel solution that we call *bridge therapy.* This work was presented at the Retina Society meeting in October, was recently published in *PLoS One,*[1] and represents collaborative work done with my retinoblastoma team of Pierre Gobin, MD; Brian Marr, MD; Ira Dunkel, MD; Scott Brodie, MD, PhD; and Jasmine Francis, MD.

EXAMINATION AND TREATMENT CHALLENGES

Just examining these children presents a challenge. Their pupils often dilate poorly, they are more sensitive to the systemic effects of topical dilating drops, and new anesthetic rules in the United States make the process tedious. Full-term babies with a postconception age of less than 45 months are now required to be kept overnight in the hospital and have 12 hours documented without apnea. If their postconception age is between 46 and 50 weeks, they are required to stay in the hospital with monitoring for 6 hours. For premature children, if their postconception age is less than 55 weeks, they are required to stay overnight.

Treatment of these children is also a challenge. Because almost all of the children (>90%) diagnosed in the first 3 months of life have the genetic form of retinoblastoma, they are especially sensitive to the damaging effect of ionizing radiation. We first demonstrated (and others confirmed) that external beam irradiation of children in the first year of life increases the incidence of second nonocular cancers by 2- to 8-fold. Giving systemic chemotherapy is also a problem.

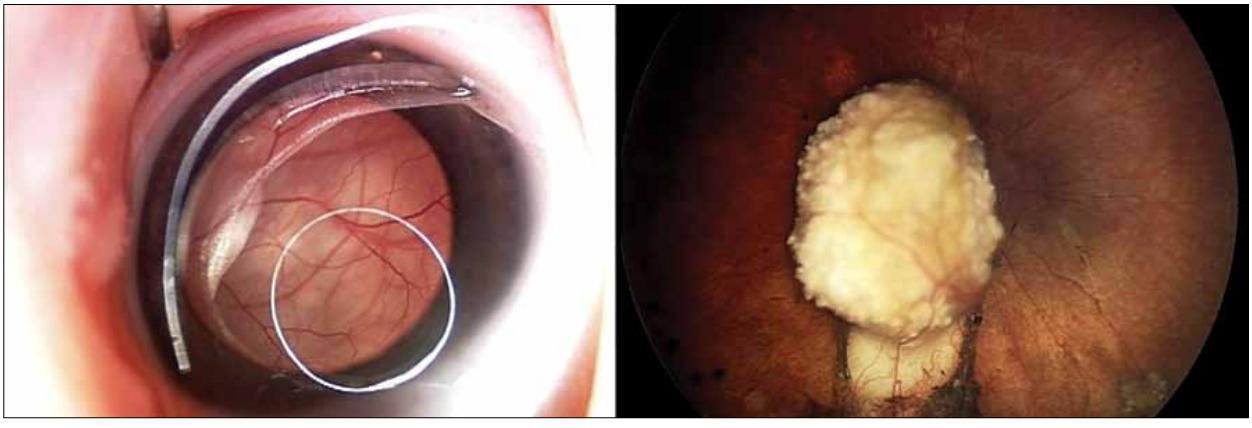

Figure 1. Before (left) and after (right) successful bridge therapy for advanced retinoblastoma with retinal detachment.

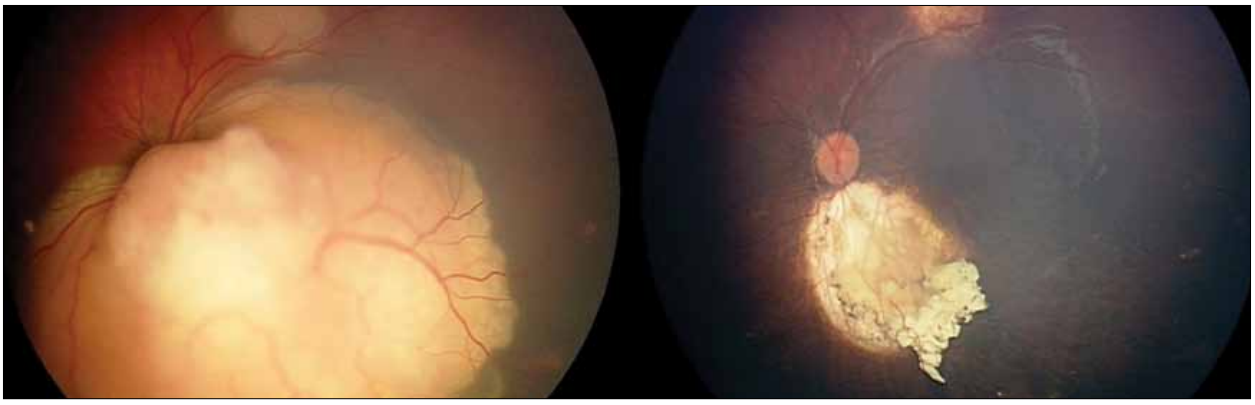

Figure 2. Before (left) and after (right) successful bridge therapy.

The children usually require ports and are at risk for port infections, often associated with fever and/or neutropenia requiring emergency hospitalization and treatment. Multidrug systemic chemotherapy often requires transfusions, which are also a challenge in these young children. Because their renal clearance changes daily during this time (and many chemotherapeutic agents used for retinoblastoma are cleared by the kidneys) dosing drug is imprecise and the effects and side effects unpredictable. Radioactive plaques do not exist in most centers that fit these smaller eyes, and laser and cryotherapy are challenging because of the size of the eye.

Indeed, prior studies of success of managing retinoblastoma in the first 3 months of life highlight these challenges. Just 10 years ago we published on the largest series of children treated in the first month of life. Despite the diagnosis of retinoblastoma at a mean of 18 days, 19% of the eyes came to enucleation, 8.7% of the children died of metastatic disease, and 54% of children had second nonocular cancers by the age of 23 years.

CHILDREN YOUNGER THAN 3 MONTHS

Intrarterial chemotherapy (now called ophthalmic artery chemosurgery) in our center and most major centers worldwide has largely replaced the use of systemic chemotherapy or external beam radiation but is not an option for children in the first 3 months of life. Because of the small size of the femoral artery and the risk of femoral artery occlusion, it is rarely performed before the age of 3 months or with less than 6 kg weight.

The concept of bridge therapy is straightforward. Treat the existing tumor(s) with modest doses of single-agent chemotherapy a few times until the child is old enough to get definitive and curative ophthalmic artery chemosurgery. Use diode laser and or cryotherapy for treatable tumor foci. This avoids the need for multiagent chemotherapy, avoids need for a port (with related infections and need for transfusions), avoids radiation, and can be done as outpatient procedures.

We recently reported on this approach at Memorial Sloan-Kettering Cancer Center in 19 eyes of 11 children. All children are alive, and no child developed either metastatic disease or a second cancer. As expected, 10 of the 11 children had the genetic form of the disease, and 9 were bilateral. Our mean follow-up was more than 2 years. Despite the young age, half the eyes had Reese-Ellsworth classification IV or V and almost 40% had International Classification of Retinoblastoma D or E. Eighteen of the 19 eyes were salvaged and final 30 Hz flicker electroretinograms were better than 75 uV in 74% of cases. All retinal detachments resolved with treatment. Figure 1 represents such a case.

Five of the 19 eyes received an average of only 2 doses of single agent carboplatin (1 hour infusion on an outpatient basis) and were then cured with only supplemental diode laser therapy and/or cryotherapy. One eye in a developmentally delayed child with 13q deletion syndrome was enucleated after a poor response to carboplatin.

Of the remaining eyes that received systemic carboplatin first ,100% of the eyes could be salvaged after a mean of 3.5 outpatient ophthalmic artery treatments. Figure 2 demonstrates successful treatment of retinoblastoma that resulted in salvaging vision.

Bridge therapy offers clinicians a safe and effective way to manage retinoblastoma in the first 3 months of life that saves lives, eyes, and vision with better results than prior management strategies. ■

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1. Gobin YP, Dunkel IJ, Marr BP, Francis JH, Brodie SE, Abramson DH. Combined, sequential intravenous and intra-arterial chemotherapy (bridge chemotherapy) for young infants with retinoblastoma. *PLoS One*. 2012;7(9):e44322.