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Triple-drug chemotherapy with topotecan helps preserve vision in retinoblastoma patients

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Revamping front-line multi-drug chemotherapy for retinoblastoma to include topotecan helped to maintain high cure rates for the eye cancer while preserving patients' vision and reducing their risk of treatment-related leukemia. Results of the St. Jude Children's Research Hospital study appear online today in the *Journal of Clinical Oncology*.

"This 10-year follow-up study shows for the first time that topotecan can be used in front-line therapy to help reduce exposure of retinoblastoma patients to etoposide, which is associated with secondary leukemia," said first and corresponding author Rachel Brennan, M.D., an assistant member of the St. Jude Department of Oncology. "We expected patients to be cured, but we also found more than 80 percent of patients had measurable vision."

Retinoblastoma is a malignant tumor that begins in the retina, the light-sensing tissue at the back of the eye. It is diagnosed in 250 to 300 children annually in the U.S.; most are less than 2 years old when the tumor is discovered.

For retinoblastoma patients in the U.S. whose disease is confined to the eye, the cure rate exceeds 95 percent. But the widely used triple-drug chemotherapy designed to help preserve the eyes and vision of retinoblastoma patients includes etoposide, a drug that leaves survivors at risk for acute myeloid leukemia.

More than 10 years ago, the need for safer, more effective retinoblastoma therapy led Michael Dyer, Ph.D., chair of the St. Jude Department of Developmental Neurobiology, to begin the laboratory research that laid the foundation for this study. Topotecan had shown promise in treatment of other solid tumors, including brain tumors. This encouraged the study's senior authors Carlos Rodriguez-Galindo, M.D., of St. Jude, and Matthew Wilson, M.D., of St. Jude and the University of Tennessee Health Science Center (UTHSC), to work with Dyer on preclinical testing of topotecan.

Working with retinoblastoma tumor cells growing in the laboratory and in mice, Dyer confirmed that topotecan was a possible replacement for etoposide in retinoblastoma therapy and determined the effective dose. The laboratory findings led to a prospective clinical trial in newly diagnosed, bilateral retinoblastoma patients.

"The results in this study are the culmination of a true team effort," Brennan said. "The findings are a shining example of the St. Jude bench-to-bedside approach to developing new therapies that focus on the life-long health of the whole patient."

The study included 26 children with advanced, bilateral retinoblastoma that had not spread beyond their eyes.

Rather than standard combination chemotherapy with vincristine, carboplatin and etoposide, the patients were treated with vincristine, topotecan and carboplatin. Thermotherapy, cryotherapy and other focal therapies were used as necessary to destroy small tumors that remained in patient eyes as therapy progressed.

The triple-drug chemotherapy with topotecan was more successful than standard chemotherapy at avoiding surgical removal of an eye or the use of external beam radiotherapy to stop disease progression. Seventy-eight

percent of the 51 advanced disease eyes included in the study analysis were salvaged with treatment that included topotecan. That compares to previous reports of 30 to 60 percent following chemotherapy that included etoposide and often required radiotherapy. Altogether, 10 eyes in 26 patients were surgically removed, including one eye removed at diagnosis prior to chemotherapy and three removed after radiation therapy failed to stop disease progression.

"Preservation of an eye is not synonymous with preservation of vision," Brennan said. "But this therapy provided significant improvement in survival of eyes and useful vision in patients with advanced retinoblastoma."

Regular vision screening of survivors identified 18 patients with vision of 20/40 or better in at least one eye. The World Health Organization defines mild vision loss and near normal vision as corrected vision of 20/30 to 20/60 in at least one eye.

Brennan said this study showed that incorporating topotecan into front-line therapy of patients with advanced localized disease improves survival of eyes with useful vision. Meanwhile, research continues at St. Jude to maximize the benefit of chemotherapy for the treatment of retinoblastoma as well as the route of delivery.

Provided by St. Jude Children's Research Hospital

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