Avoiding specific region of brain during whole-brain radiotherapy prevents memory loss

Atlanta, September 23, 2013—Limiting the amount of radiation absorbed in the hippocampal portion of the brain during whole-brain radiotherapy (WBRT) for brain metastases preserves memory function in patients for up to six months after treatment, according to research presented today at the American Society for Radiation Oncology’s (ASTRO’s) 55th Annual Meeting.

The single-arm, phase II study was a multi-institutional, international clinical trial in the U.S. and Canada, conducted through the Radiation Therapy Oncology Group (RTOG). Researchers compared the study group to a historical control group of patients who had received WBRT without hippocampal avoidance in the PCI-P-120-9801 phase III trial (Li 2007).

This study enrolled 113 adult patients from 2011 through 2013 who had a measurable brain metastasis outside a 5-mm margin around the hippocampus. Of those patients, 100 were analyzable and 76 percent were categorized as recursive partitioning analysis (RPA) class II. All patients received hippocampal avoidance whole-brain radiotherapy (HA-WBRT) to 30 Gy in 10 fractions. In all analyzable patients, the dose received by the entirety of the hippocampus did not exceed 10 Gy, and the maximum dose did not exceed 17 Gy. Patients were assessed using the Hopkins Verbal Learning Test - Delayed Recall (HVLT-DR), the HVLT - Recall (HVLT-R) and the HVLT - Immediate Contact.
Recognition (HVLT-IR) at baseline and post-treatment at two-, four- and six-month intervals. The primary endpoint of the trial was the HVLT-DR at four months.

Results showed that the 42 patients who were analyzable at four months post-RT had a seven percent decline in HVLT-DR from baseline to four months (95 percent confidence interval (CI): -4.7 percent to 18.7 percent). This is statistically significant when compared to the historical control group (p=0.0003), which demonstrated a 30 percent decline in HVLT-DR at four months. Six months after treatment, the 29 analyzable patients had a two percent decline in HVLT-DR from baseline (95 percent CI: -9.2 percent to 13.1 percent).

“Radiotherapy to the brain is known to impact the memory function of cancer survivors,” said Vinai Gondi, MD, lead author of the study, Co-Director of the Cadence Brain Tumor Center and Associate Director of Research at the Cadence Proton Center in Warrenville, Ill, and Clinical Assistant Professor at the University of Wisconsin School of Medicine and Public Health in Madison, Wis. “A compartment of neural stem cells located in the hippocampus, sensitive to radiotherapy and important for memory function, is thought to be central to these effects. Our research group developed advanced radiotherapy techniques that spare this hippocampal neural stem cell compartment from significant radiation doses. The study results were statistically better than historical data of whole-brain radiotherapy without hippocampal sparing and present a number of opportunities to introduce hippocampal sparing in other contexts of radiotherapy to the brain. The RTOG is currently developing phase III trials to explore these other contexts and to validate these results.”

The abstract, “Memory Preservation with Conformal Avoidance of the Hippocampus during Whole-Brain Radiotherapy (WBRT) for Patients with Brain Metastases: Primary Endpoint Results of RTOG 0933,” will be presented in detail during the Plenary session at ASTRO’s Annual Meeting at 2:00 p.m. Eastern time, on Monday, September 23, 2013. To speak with Dr. Gondi, call Michelle Kirkwood on September 22 - 25, 2013, in the ASTRO Press Office at the Georgia World Congress Center in Atlanta at 404-222-5303 or 404-222-5304, or email michellek@astro.org.
ASTRO’s 55th Annual Meeting, held in Atlanta, September 22-25, 2013, is the premier scientific meeting in radiation oncology and brings together more than 11,000 attendees including oncologists from all disciplines, medical physicists, dosimetrists, radiation therapists, radiation oncology nurses and nurse practitioners, biologists, physician assistants, practice administrators, industry representatives and other health care professionals from around the world. The theme of the 2013 meeting is “Patients: Hope • Guide • Heal” and focuses on patient-centered care and the importance of the physician’s role in improving patient-reported outcomes and the quality and safety of patient care. The four-day scientific meeting includes presentation of four plenary papers, 363 oral presentations, 1,460 posters and 144 digital posters in 70 educational sessions and scientific panels for 19 disease sites/tracks. Keynote and featured speakers include: William B. Munier, director of the Center for Quality Improvement and Patient Safety at the Agency for Healthcare Research and Quality; Darrell G. Kirch, MD, president and CEO of the Association of American Medical Colleges; James Cosgrove, PhD, director of the U.S. Government Accountability Office; Otis W. Brawley, MD, chief medical officer of the American Cancer Society; and Peter Friedl, MD, PhD, of St. Radboud University Nijmegen Medical Centre at the University of Nijmegen and MD Anderson Cancer Center.

ABOUT ASTRO

ASTRO is the premier radiation oncology society in the world, with more than 10,000 members who are physicians, nurses, biologists, physicists, radiation therapists, dosimetrists and other health care professionals that specialize in treating patients with radiation therapies. As the leading organization in radiation oncology, the Society is dedicated to improving patient care through professional education and training, support for clinical practice and health policy standards, advancement of science and research, and advocacy. ASTRO publishes two medical journals, International Journal of Radiation Oncology • Biology • Physics (www.redjournal.org) and Practical Radiation Oncology (www.practicalradonc.org); developed and maintains an extensive patient website, www.rtanswers.org; and created the Radiation Oncology Institute (www.roinstitute.org), a non-profit foundation to support research and education efforts around the world that
enhance and confirm the critical role of radiation therapy in improving cancer treatment. To learn more about ASTRO, visit www.astro.org.
LBA1  Memory Preservation with Conformal Avoidance of the Hippocampus during Whole-Brain Radiotherapy (WBRT) for Patients with Brain Metastases: Primary Endpoint Results of RTOG 0933

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Purpose/Objective(s): Hippocampal dose during WBRT has been hypothesized to play a role in cognitive decline. This may be preventable using intensity-modulated radiotherapy to conformally avoid the hippocampus during WBRT (HA-WBRT). RTOG 0933 was a single-arm phase II study of HA-WBRT for brain metastases with a primary cognitive endpoint and pre-specified comparison to a historical control of WBRT without hippocampal avoidance.

Materials/Methods: Eligible adult patients with brain metastases received HA-WBRT to 30 Gy in 10 fractions.

Hippocampal 100% dose and maximum dose could not exceed 10 Gy and 17 Gy, respectively. Standardized cognitive assessments were performed at baseline, 2, 4, and 6 months (mos). The primary endpoint was the Hopkins Verbal Learning Test Delayed Recall (HVLT-DR) at 4 mos. Secondary endpoints included HVLT Recall (HVLT-R) and Immediate Recognition (HVLT-IR). The historical control consisted of brain metastases patients treated with WBRT on the PCI-P-120-9801 phase III trial, which demonstrated a 30% mean relative decline in HVLT-DR from baseline to 4 mos. To detect a minimum relative 50% improvement, leading to an absolute 15% or less mean relative decline in HVLT-DR following HA-WBRT, 51 analyzable patients were required to ensure 80% statistical power with alpha=0.05.

Results: 113 patients were accrued from March 2011 through November 2013; 100 were eligible for analysis. 76% of patients were RPA class II. Two treatment-related grade 3 adverse events were reported (fatigue, headache); no treatment-related grade 4-5 events were observed. Median survival was 6.8 mos (95% confidence interval 95%CI) 4.8-10.9 mos). 3 patients (4.5%) had progression in the hippocampal avoidance region, consistent with expected event-rate. 42 patients were analyzable at 4 mos. Mean relative decline in HVLT-DR from baseline to 4 mos was 7.0% (95%CI: -4.7% to 18.7%), which was significant in comparison to the historical control (p=0.0003). Mean relative decline in HVLT-R and HVLT-IR from baseline to 4 mos was 3.6% (95%CI: -2.9% to 10.1%) and 1.6% (95%CI: -2.8% to 6.0%), respectively. 29 patients were analyzable at 6 mos with a mean relative decline in HVLT-DR, HVLT-R and HVLT-IR from baseline to 6 mos of 2.0% (95%CI: -9.2% to 13.1%), -3.0% (95%CI: -12.0% to 5.9%) and 0.7% (95%CI: -3.1% to 4.4%), respectively.

Conclusions: Conformal avoidance of the hippocampus during WBRT is associated with memory preservation at 4 and 6 mos follow-up. These phase II results compare favorably to historical series and warrant further validation in a phase III trial, currently under development in the RTOG.

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