ASTRO
TARGETING CANCER CARE

News Release

Contact: Liz Gardner liz.gardner@astro.org Erin Boyle erin.boyle@astro.org

Clinical review explores role of RT in BRCA1, BRCA2 mutation breast cancer treatment

FAIRFAX, Va., March 7, 2016 – In light of conflicting and inconclusive clinical data on the benefit of radiation therapy in cancer patients with the BRCA1 and BRCA2 mutation, a clinical review examined the current status of data regarding BRCA1 and BRCA2 deficiency and radiation therapy sensitivity and a potential strategy to intensify the effects of radiation therapy (RT) by poly(ADP-ribose) polymerase inhibitors (PARPi), the pharmacologic drugs under investigation as monotherapy for the treatment of breast cancer in patients with BRCA1 and BRCA2 mutations.

Authors Junran Zhang, MD, PhD, and Charlene Kan, MD, PhD, Department of Radiation Oncology, Case Western Reserve University School of Medicine, Cleveland, Ohio, and University Hospitals Seidman Cancer Center, Cleveland, found mixed results from clinical and laboratory research into the sensitivity of cancer cells with the BRCA1 and BRCA2 mutation in their clinical review, "BCRA1 Mutation: A Predictive Marker for Radiation Therapy?" The review was published in the *International Journal of Radiation Oncology • Biology • Physics* (Red Journal), the official scientific journal of the American Society for Radiation Oncology (ASTRO).

"Although there has been concern that treating patients with BRCA 1 and BRCA2 mutation with radiation could cause more toxicity and possibly increase the risk of secondary malignancies, retrospective clinical studies have not proven this," Dr. Zhang said.

Available data provides no real evidence that a genetic alteration in BRCA1 and BRCA2 has a significant role in RT-induced toxicity and secondary cancer risk, Drs. Zhang and Kan said. However, an increase in the risk of contralateral breast cancers in BRCA mutation carriers is significant.

Drs. Zhang and Kan cited numerous studies on the topic, including a multinational study by Pierce et al (77), which compared women with BRCA1 or BRCA2 mutation treated with either breast-conserving therapy and RT or mastectomy alone. In that study, Pierce and colleagues found that the local recurrence rates were higher in those treated with both breast-conserving therapy and radiation therapy (RT) (30.2 percent) at 20 years than in those treated with mastectomy (5.5 percent) at 20 years (77). No difference was noted in overall survival or regional or systemic recurrence. The risk of contralateral breast cancer was high regardless of whether adjuvant RT was given, exceeding 40 percent, suggesting that low-dose scatter from RT does not seem to increase the risk of developing breast cancer.

Drs. Zhang and Kan explained that DNA repair, including the vital double-strand break repair, is key for normal and cancer cell survival. Double-strand breaks (DSBs) are the most cytotoxic forms of DNA damage, they said. DSBs can be caused by replication stress or a principle cytotoxic lesion from ionizing radiation (IR) and radiomimetric chemicals.

BRCA1 and BRCA2 are two of the most important proteins required for homologous recombination (HR)-mediated DSBs repair, they said. Hereditary breast and ovarian cancer (HBOC) syndrome, which is related to a high risk of developing breast cancer and ovarian cancer, is due to the mutation in the BRCA1 and BRCA2 proteins.

"BRCA1 mutations lead to the sensitivity to IR. We and others have reported that BRCA1 promotes HR and non-homologous end joining (NHEJ), which are two major pathways required for repair of DSBs induced by IR. However, which DSB repair pathways controlled by BRCA1 play a more important role in the regulation of the response to IR remains unknown," Dr. Zhang said.

The concept that RT might be particularly effective in BRCA1-deficient tumors is still theoretical, she said.

"Some studies suggest these BRCA1 and BRCA2 cancers are more sensitive, which would indicate better outcomes when treated with radiation; however, others do not," she said. "The most recent studies indicate that these women benefit from radiation to the same degree as those with sporadic breast cancers."

Drs. Zhang and Kan also discussed the potential for PARP inhibition (PARPi) treatment, a hot topic in the field of DNA repair in recent years. BRCA1 cells are deficient in DSB repair, making them sensitive to DNA damaging agents. This discovery opened up the possibility of the BRCA1- and BRCA2-controlled pathways being used for more effective cancer treatment through PARP inhibition and other novel therapeutic approaches, Drs. Zhang and Kan wrote.

"As our understanding of the mechanisms and biochemical details of the role of BRCA1 in DNA damage response increases, the potential methods to target treatment for patients with BRCA1 de?ciency will emerge and will have an enormous effect on future RT and chemotherapy protocols," they said.

"Success requires the in-depth characterization of the pathways controlled by BRCA1. It will be of great interest to observe how PARPi and other novel therapeutic approaches based on the molecular pathways controlled by BRCA1 and BRCA2 affects the clinical outcomes of RT, in particular, in breast cancer treatment."

Well-funded clinical trials are needed to determine if PARPi is feasible and safe, Dr. Zhang said. Further research may also identify combinations of chemotherapy with or without radiation that may be more effective in those with BRCA1 and BRCA2 mutations.

To reach out to the study authors, contact ASTRO's Press Office at press@astro.org. For the full study, which is temporarily open for public access, visit http://www.redjournal.org/article/S0360-3016(15)00592-1/abstract. For more information about the Red Journal, visit http://www.redjournal.org.

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 three medical journals, International Journal of Radiation Oncology • Biology • Physics (www.redjournal.org), Practical Radiation Oncology (www.practicalradonc.org) and Advances in Radiation Oncology (www.advancesradonc.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.

###