

BRCA1 expression in glioblastoma multiforme tumors predicts patient survival

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Results of a study conducted by the Radiation Therapy Oncology Group (RTOG), now conducting research as NRG Oncology, are the first to show that breast cancer type 1 susceptibility gene (BRCA1) protein expression is an important predictive biomarker of overall survival in patients with glioblastoma multiforme (GBM) tumors.

The study reported today at the 56th Annual Meeting of the American Society for Radiation Oncology (ASTRO) investigated the expression and prognostic significance of four molecular biomarkers for their potential role in the formation and growth of GBM tumors. "Among the four biomarkers assessed, only BRCA1 protein expression had a statistically significant correlation with overall survival," says the study's principal investigator, Maria Vasilakopoulou, M.D., Ph.D., a medical oncologist and clinical researcher at the Pitié-Salpêtrière Hospital, in Paris, France, who carried out the research in the laboratory of David Rimm, M.D., Ph.D, a professor of pathology and medical oncology at Yale University. Specifically, patients with low tumor BRCA1 protein expression survived longer in comparison with patients with high expression of this protein, with median survival times of 18.9 versus 4.8 months, respectively.

"BRCA1 is a tumor suppressor gene that is involved in DNA repair. Mutations of this gene, or deficient protein due to epigenetic changes, lead to DNA damage repair failure. The study results suggest strongly that low BRCA1 protein expression in the GBM tumor, and the consequent low DNA repair, causes the cancer cells to be more

susceptible to DNA-damaging cancer treatment," says Vasilakopoulou, "Moreover, as BRCA1 seems to be a predictive biomarker of unfavorable survival in GBM, patients identified as high expressers could be treated with agents that downregulate BRCA1 thus sensitizing them to other cytotoxic therapies."

Despite advances in surgery, radiation therapy, and chemotherapy, patients with newly diagnosed GBM have a poor prognosis, with a median survival of 14 to 16 months. Vasilakopoulou suggests that genetic alterations can be helpful, not only for prognostication, but also in serving as targets for directed therapies. "Targeting BRCA1 is a promising therapeutic strategy and several agents such as PARP-inhibitors may target BRCA1 leading to failure of DNA damage repair and apoptosis preferentially in BRCA1-defective cells," says Vasilakopoulou, who points out that the FDA's recent approval of a PARP inhibitor for BRCA-mutated ovarian cancer, combined with the ongoing research for this new class of targeted therapy, render this therapeutic strategy an attractive option that may be beneficial to some groups of patients. Further work is needed, both in vitro and in clinical trials, to evaluate the correlation between BRCA1 expression and response to these targeted therapies. The next step is to validate these results on another cohort. Planning is underway for such a validation study.

"These results suggest that BRCA1 testing could play a future role in the development of more individualized treatment options for patients whose tumor genetic profile shows low BRCA1 protein expression," says senior abstract author Jonathan Knisely, M.D., Chief of the Division of Radiosurgery and Stereotactic Program in the Radiation Medicine Department at the North Shore-LIJ Cancer Institute in Lake Success, N.Y. and Associate Professor at Hofstra North Shore-LIJ School of Medicine.

The investigators analyzed tissue microarrays composed of archived glioblastoma tumors from 66 patients who participated in one of nine different RTOG clinical trials. The [patients](#) had similar overall survival and were treated with surgery, radiation, and non-temozolomide chemotherapy. The RAD51, BRCA1, PTEN, and miRNA-210 [protein expression](#) levels were assessed using in situ hybridization and automated quantitative protein analysis (AQUA).

"The study results add another important piece of information to our understanding of this lethal cancer and build on the extensive prior work of NRG Oncology to identify glioblastoma tumor markers relevant to treatment planning and prognosis," says Walter J. Curran Jr., M.D., who is an abstract author and an NRG Oncology Group Chairman and Executive Director of the Winship Cancer Institute of Emory University in Atlanta.

Provided by NRG Oncology

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