KRAS gene mutation and amplification status affects sensitivity to antifolate therapy

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Testing patients with non-small cell lung cancer for both mutations and amplifications of the KRAS gene prior to therapy may help to predict response to treatment with antifolates, according to the updated results of a preclinical study presented at the AACR Annual Meeting 2012, held here March 31 - April 4.

Patients, especially those with lung cancer, who have KRAS gene mutations have a worse prognosis and do not respond well to targeted therapies, according to Sarah Bacus, Ph.D., Quintiles senior vice president and chief scientific officer of translational research and development, oncology. The results suggest that although these mutations are linked to a poor response to targeted therapies, they may predict response to treatment with antifolates, as long as the number of mutant genes is not amplified.

She and her colleagues assessed the relationship between antifolate medications and KRAS mutations and amplification, where the gene has an excess number of copies.

The preliminary results of the study were presented in November at the AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics. Researchers treated human non-small cell lung cancer cell lines (KRAS wild type, KRAS-mutant nonamplified and KRAS-mutant amplified) with the antifolates methotrexate or pemetrexed.

In lung cancer, the KRAS-mutant tumors need the folate pathway, which is associated with the growth of cancer. Treatment with the antifolate pemetrexed led to dramatic responses in patients with KRAS-mutant lung cancer. Patients with KRAS-wild type were less responsive. The researchers found a similar trend in KRAS-mutant lung cancer cell lines. When cell lines with KRAS mutations were deprived of access to this pathway, they failed to grow. However, this response was not seen if the number of copies of the KRAS-mutant gene was amplified or if the KRAS was wild type.

"KRAS mutations are most frequently observed in pancreatic, colorectal, lung, endometrial and biliary tract cancers, and as such, antifolates may have utility in the treatment of these cancers alone or in combination with other chemotherapies such as DNA-damaging agents," Bacus said.

She recommended that before prescribing an antifolate, whether in lung cancer or other cancers where KRAS mutations are prevalent, physicians should test for KRAS mutation and amplification, because the study results suggest that patients are likely to respond well only if the KRAS gene is mutated and not amplified.

More information: KRAS mutation and amplification status predicts sensitivity to antifolate therapies in Non Small Cell Lung Cancer

Abstract
Somatic genetic mutation in the V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (KRAS) gene has been linked to poor prognosis and resistance to various targeted therapeutics in Non Small Cell Lung Cancer (NSCLC). Therapeutic strategies that target tumors harboring these mutations represent an unmet medical need. In this study, we investigated the relationship between antifolate sensitivity and KRAS mutation/amplification status in NSCLC.
Human NSCLC cell lines (KRAS wild type, KRAS mutant non-amplified and KRAS mutant amplified) were treated with Methotrexate (MTX) or Pemetrexed (PEM) and assayed for proliferation. In these studies, KRASwt (wildtype) and KRASmut

(mutant) amplified cells showed resistance to MTX treatment (IC50 >10?M). In contrast, growth of all KRASmut non-amplified cell lines studied was inhibited with MTX treatment (IC50