Patients with aberrations in two genes respond better to drugs blocking a well-known cancer pathway

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Cancer patients with mutations or variations in two genes -– PIK3CA and PTEN -– who have failed to respond to several, standard treatments, respond significantly better to anti-cancer drugs that inhibit these genes' pathways of action, according to research presented at the 24th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Dublin, Ireland, today.

Dr Filip Janku (MD, PhD), assistant professor in Investigational Cancer Therapeutics at MD Anderson Cancer Center (Houston, USA), told the meeting that mutations in PIK3CA and aberrations (loss of function or mutation) in PTEN were present in a wide range of tumours and were thought to be involved in the development of cancer. These genes act via a pathway known as the PI3K/AKT/mTOR pathway, and so inhibiting the pathway could improve the patients' response to treatment.

The researchers tested 1656 patients with a variety of cancers and found that 146 (9%) had PIK3CA mutations, 150 (13%) had PTEN aberrations and 14 (1%) had both.

They treated 134 of the patients who had PIK3CA mutations, PTEN aberrations or both in early-phase clinical trials that included drugs that block the PI3K/AKT/mTOR pathway. The patients had failed an average of three, previous treatments. Of these patients, 107 were also tested for mutations in another, known cancer-causing gene, KRAS.

Dr Janku said: "We found that heavily pre-treated patients with PIK3CA mutations, PTEN aberrations, or both had a significantly higher response rate on protocols incorporating PI3K/AKT/mTOR inhibitors compared to patients without known PIK3CA/PTEN aberrations treated on the same protocols. In addition, we noticed that patients who had these and also simultaneous mutation in codons 12 or 13 of KRAS (which is a likely mechanism of drug resistance) did not respond to protocols with PI3K/AKT/mTOR inhibitors.

"Furthermore, it looks as if treatment with a single agent may not be sufficient, as patients with PIK3CA mutations and/or PTEN aberrations treated with drug combinations that included PI3K/AKT/mTOR inhibitors had higher response rate than patients treated with PI3K/AKT/mTOR inhibitors alone."

Of the patients who were treated with PI3K/AKT/mTOR inhibitors, 23 out of 134 (17%) had a partial response to the therapy (where the tumour shrinks by at least 30%) and 9 out of 134 (7%) had stable disease for six months or more, while only 26 out of 458 patients (6%) without a PIK3CA mutation or PTEN aberration had a partial response when treated with the same therapies. Of the 26 patients who also had a KRAS mutation in codons 12 or 13, only one (4%) had a partial response, compared to 18 out of 81 (22%) of patients without the KRAS mutation. Among the patients treated with a single agent, PI3K/AKT/mTOR inhibitor, only one out of 40 (2.5%) had a partial response to the treatment compared to 22 out of 94 (23%) of the patients treated with a combination of agents, including a PI3K/AKT/mTOR inhibitor.

Dr Janku said: "These results suggest that heavily pre-treated patients with mutations or aberrations in PIK3CA, PTEN or both are more likely to have tumours that respond and shrink when they are treated with a combination of drugs that include PI3K/AKT/mTOR inhibitors, compared with patients treated the same way but whose PIK3CA and PTEN status is unknown. Therefore, screening for

these mutations and aberrations, as well as KRAS mutations, can make treatments with PI3K/AKT/mTOR inhibitors more effective for patients."

He said that further investigation was required as the study had several limitations that included the fact that the patients had a variety of cancers, received diverse treatments, were treated on different dose levels and the study was not randomised. "Our findings warrant further prospective investigation especially since many PI3K/AKT/mTOR inhibitors are entering the clinical arena."

There are a number of PI3K/AKT/mTOR inhibitors currently being developed; however, none of the ones that inhibit the PI3K or AKT have been approved yet for use in the clinic. Examples of mTOR inhibitors that have been approved for treatment of cancers include temsirolimus and everolimus.

Professor Stefan Sleijfer, the scientific chair of the EORTC-NCI-AACR Symposium, from Erasmus University Medical Centre (The Netherlands), commented: "This study is interesting because it provides important hints as to how we can select cancer patients who are likely to benefit from PI3K /AKT/mTOR inhibitor-containing regimens. If confirmed, this may be the way to come to a more personalised treatment approach with these compounds."

More information: Abstract no: 246. Proffered papers, plenary session 6, 15.00 hrs, Thursday 8 November.

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