Medical Xpress

Promising results from new drug combination in patients with advanced solid tumors

November 30 2016

Munich, Germany: An experimental drug called TAS-114, which has the potential to increase the anti-cancer effects of chemotherapy without increasing adverse side effects, has shown promising results in patients with hard-to-treat cancers in a phase I clinical trial.

In a presentation at the 28th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Munich, Germany, today (Thursday) Dr Takekazu Aoyama, a surgeon and vice president of clinical development at Taiho Oncology Inc, Princeton, USA, described how TAS-114 in combination with another chemotherapy caused tumours to shrink in patients with advanced non-small cell lung cancer, pancreatic cancer, colorectal cancer and breast cancer. In addition, some patients whose cancer had failed to respond to other therapies were able to continue with the treatment and their disease remained stable without progressing for more than six months.

TAS-114 inhibits deoxyuridine triphosphatase (dUTPase)—a 'gatekeeper' protein that acts on FdUTP, a metabolite of the anti-cancer drug 5-fluorouracil (5-FU), and restricts its incorporation into the DNA of cancer cells, thereby enabling the cells to continue living and proliferating. Research has already shown that tumours with high levels of dUTPase are resistant to 5-FU chemotherapy, and so successful inhibition of dUTPase may be an important step in enhancing the activity of 5-FU.

In the study presented today, researchers from Italy, Switzerland, France and Belgium, enrolled 92 patients into a phase I trial in which TAS-114 was given to patients together with a chemotherapy called S-1, which is a fixed-dose combination of tegafur, gimeracil and oteracil. Tegafur is the active anti-cancer agent, which, after administration, is converted by the body into the active form of 5-FU; gimeracil inhibits the degradation of 5-FU, leading to higher 5-FU levels in the body for longer; and oteracil inhibits activation of 5-FU in the gut, resulting in lower toxic side effects there, such as diarrhoea.

TAS-114 and S-1 were given orally twice a day for 14 days before food, followed by seven days rest before repeating. The doses ranged from a starting dose of 5 mg/m2 (TAS-114) and 25 mg/m2 (S-1) up to 240 mg/m2 and 36 mg/m2 respectively. The trial aimed to determine the maximum tolerated dose and the recommended dose, while also looking at how well the drugs worked against the tumours and how they interacted with the body (pharmacokinetics and pharmacodynamics). In addition to the cancers already mentioned, patients with cancers of the liver, biliary tract, endometrium and stomach were included.

The most recent data from the trial presented at the Symposium showed that 15 of the patients were able to continue receiving the treatment for more than six months without their disease progressing. In addition, tumour responses were observed in three of the patients with non-small cell lung cancer, one with pancreatic cancer, one with breast cancer and one with colorectal cancer.

Dr Aoyama said: "These results show favourable responses across all the tumour types and they were particularly outstanding in patients with non-small cell lung cancer where we saw robust partial tumour responses and good disease control rates. We consider that to be able to control disease for a period as long as six months and beyond provides a significant clinical benefit to patients who had all been previously heavily treated.

"In addition, we saw no additional toxic side effects in patients who were given the drug combination above what is expected with S-1 alone. Patients tolerated the treatment well and the side effects were manageable. These findings warrant further investigation of the drug combination in a phase II clinical trial."

Provided by ECCO-the European CanCer Organisation

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