MedicalXpress

Results from three ground-breaking cancer studies show early benefit to patients

November 30 2016

The "revolution in the understanding of cancer at the molecular level" has led to dramatic responses in cancer patients to new therapies that are targeted precisely at their particular type of tumours, according to an expert.

Dr Kapil Dhingra, a member of the executive committee for the 28th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics that is taking place in Munich, Germany, told the meeting today (Thursday): "We are seeing an important shift in oncology as we move from a one-treatment-fits-all approach to an era of personalised medicine for cancer. In this new era it is essential to discover novel, targeted drugs and to identify the patients most likely to benefit from them. This is highlighted at this meeting by several new drugs that show dramatic efficacy in patients with very advanced disease who have failed standard therapies. These drugs can be developed rapidly, based on trials involving relatively small numbers of patients.

"At the same time, advances in liquid biopsy technologies, in which blood is taken and analysed to detect genetic mutations, allow clinicians and researchers to obtain a real time portrait of the patients' cancers and their responses to treatment in a non-invasive way, thereby ushering in a new era of cancer therapeutics."

Dr Dhingra, who is managing member of KAPital Consulting LLC (USA), highlighted several presentations at the meeting that show how new drugs can be very effective when targeted at cancers with the right

molecular profile, and how liquid biopsies can accurately identify mechanisms of resistance in patients receiving targeted therapies. These include:

1. 'Remarkable anti-tumour activity' from an ongoing Phase I study of a new drug, BLU-285, that targets specific mutations in the cancer-causing genes that drive rare sarcomas of the digestive system (gastrointestinal stromal tumours or GISTs)

More than 85% of GISTs are driven by specific mutations in cancer-causing genes (oncogenes) called KIT and PDGFRα. These genes provide instructions for making proteins that are part of a family of proteins called receptor tyrosine kinases, which are involved in cell signalling. When the genes are mutated the signalling malfunctions, leading to cell proliferation and cancer. There is no effective treatment for GISTs at present and although imatinib (a tyrosine kinase inhibitor) can provide some benefit initially, most patients will eventually experience disease progression, often driven by genetic changes known as "secondary activation loop mutations". These activation loop mutations are often resistant to all approved kinase inhibitors.

In an ongoing phase I trial, 36 patients (as of 1 November 2016) who had advanced GISTs with mutations in either KIT or PDGFRα, some of whom had cancer that had continued to advance despite at least two previous treatments with tyrosine kinase inhibitors such as imatinib, were given BLU-285 once a day on a continuous schedule at doses ranging from 30 to 400 mg a day. BLU-285 is the first drug to selectively target activation loop mutations.

Professor Michael Heinrich (MD) from Oregon Health and Science University (USA), told the Symposium: "Although we are still increasing

the doses in the phase I trial to establish the recommended dose, BLU-285 has shown remarkable anti-tumour activity, with a response seen at the lowest dose level. CT and MRI scans showed that tumours shrank in 14 out of 15 evaluable PDGFRα patients and five out of 13 evaluable KIT patients. In addition, there was a more than ten-fold reduction in levels of PDGFRα-mutated DNA circulating in the blood, and we saw this even before the imaging scans confirmed that tumours were shrinking. The treatment was well tolerated to date and 27 patients continue to be treated in the study, while nine discontinued treatment due to their disease progressing."

Dr Dhingra said: "The data from this study to date show that GISTs with PDGFRα and KIT mutations, including activation loop muations, are sensitive to BLU-285, a potent and highly selective tyrosine kinase inhibitor. Preliminary clinical efficacy has been seen, even at very low doses, and it is active in patients with advanced disease, many of whom had disease that had progressed on previous treatments. Liquid biopsies showed a large reduction in circulating tumour DNA within two weeks of starting treatment."

2. 'DCC-2618 is one of the most active compounds I have seen in the phase I setting in my career.' Impressive activity seen in GIST patients and a patient with brain cancer with a broad range of alterations in KIT and PDGFRA genes.

A new drug called DCC-2618 targets the same oncogenes in GIST as BLU-285, but a broader range of alterations in these genes. It is being tested in a phase I trial in patients with advanced GIST and other advanced cancers including one patient with glioblastoma multiforme (GBM) - one of the most common and aggressive forms of brain cancer. Patients with molecular alterations in KIT or PDGFRA genes were

prioritised for enrolment in the trial. So far, 25 patients have been enrolled but the researchers are hoping to recruit more, including patients with cancers other than GIST that have alterations in KIT or PDGFRA genes.

Filip Janku, assistant professor in the Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center (USA), told the meeting: "While it is early, we observed signs of benefit in the GIST patients treated whose disease had progressed despite multiple previous treatments. Early partial metabolic responses, a sign of reduced tumour metabolic activity, were observed in 14 of the 15 patients evaluated with KIT-mutant GIST.

"In addition to GIST, we sought to evaluate patients with other genetically defined cancers that might also benefit from treatment with DCC-2618. For example, the first patient enrolled in the trial had a GBM with simultaneous alterations in KIT and PDGFRA genes. This patient began to demonstrate improvements relatively early in treatment as the tumour shrank slowly but steadily, and today, more than 12 months later, the patient is continuing to do well. We are very excited to see the response in this patient as it is a very hard cancer to treat.

"DCC-2618 is well tolerated by patients and the anti-tumour activity observed to date suggest that it is effectively inhibiting the tyrosine kinases that we are targeting. The findings are very encouraging in that they support a shift in oncology drug development toward targeted therapies, such as DCC-2618, in genetically-defined patient populations beginning as early as phase 1 clinical trials. This is important as it provides information early in the clinical development process to help define patient populations that might potentially benefit.

"In this study, we also employed a novel next-generation sequencing technology to identify and dynamically track molecular alterations in

tumour-derived circulating cell-free DNA isolated from blood of treated patients in order to understand the molecular basis of response, and intrinsic or adaptive resistance to DCC-2618.

"DCC 2618 is one of the most active compounds I have ever seen in the phase I setting in my career."

Dr Dhingra said: "Even though the phase I dose escalation is ongoing, impressive early results have been seen, including in the difficult-to-treat site of the brain. Liquid biopsies have revealed in real or near-real time the presence of multiple mutations, reflecting a diversity in the genetic make-up of the tumours that might have been missed even if an invasive tissue biopsy had been done, which is traditionally considered to be the 'gold standard'."

The researchers are testing dose levels ranging from 20 mg to 150 mg in patients (taken orally twice a day over a 28-day cycle). Once the maximum tolerated dose has been identified, they plan to recruit groups of patients with a range of other cancers that have the KIT or PDGFRα mutations identified in this phase of the trial.

3. Patient-friendly liquid biopsies successfully identify molecular alterations driving drug resistance in nearly 80% of patients. Study shows how 'liquid biopsy will change the practice of oncology in the coming years'.

Professor Ryan Corcoran, Translational Research Director, Center for Gastrointestinal Cancers, Massachusetts General Hospital Cancer Center (USA), told the meeting: "To understand how gastrointestinal (GI) cancers develop resistance to targeted therapies, we employed a systematic 'liquid biopsy' programme within the GI cancer centre at

Massachusetts General Hospital, by which blood was collected at the time that a patient's disease stopped responding to treatment and the disease started to progress. Circulating tumour DNA was analysed by next-generation sequencing to identify mutations that emerged during therapy to drive resistance to treatment.

"Circulating tumour DNA is shed by tumour cells throughout the body into the bloodstream and can be isolated from a routine blood draw. Since tumour cells residing in different metastatic tumour lesions in the same patient can often evolve distinct mechanisms of drug resistance, 'liquid biopsy' analysis of circulating tumour DNA can frequently identify the simultaneous presence of multiple resistance alterations that would be missed by a single-lesion tumour biopsy.

"In 31 patients, this liquid biopsy programme identified a molecular alteration driving resistance in nearly 80% of patients, and half of these patients were found to have multiple alterations detectable in the blood. In patients in whom biopsies of the tumour had also been taken at the time that their disease started to progress, liquid biopsy identified additional alterations 62% of the time. Systematic liquid biopsy also led to the discovery of several novel mechanisms of resistance, which can help guide the development of therapeutic strategies to overcome resistance. Overall, these data show how routine clinical implementation of liquid biopsy at the time of disease progression on targeted therapy can effectively identify important mechanisms of resistance and may offer certain advantages relative to tumour biopsies.

"One of the biggest advantages of liquid biopsies is that they can be performed from a routine blood draw, sparing patients the necessity of undergoing costly and invasive tumour biopsies, which can also pose some procedural risks for patients. Furthermore, liquid biopsies may better capture 'tumour heterogeneity', or the evolution of distinct resistance mechanisms in different tumour cells in independent

metastases in the same patient, which might be missed by a needle biopsy of a single tumour lesion."

Chair of the scientific committee for the Symposium, Professor Jean Charles Soria from the Institut Gustave Roussy (France) told the meeting: "Liquid biopsies are a patient-friendly approach to obtaining critical insight into the intrinsic tumour biology in any given patient. In this case, they have allowed rapid and robust identification of the mechanism of acquired resistance that can help clinicians to select further therapies for the patient.

"This study shows very clearly how liquid biopsy can change the practice of oncology in the coming years."

Provided by ECCO-the European CanCer Organisation