Real-world targeted treatment based on whole genome sequencing difficult in pancreatic cancer

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Although advances in whole genome sequencing have made it possible to identify unique druggable alterations in individual tumors, real-world application of this technology in diseases such as pancreatic cancer remains a challenge, according to research from the Individualized Molecular Pancreatic Cancer Therapy (IMPaCT) trial presented here at the AACR Annual Meeting 2015, April 18-22.

This study is being simultaneously published in *Clinical Cancer Research*, a journal of the American Association for Cancer Research.

The IMPaCT trial was designed to use whole genome sequencing of pancreatic cancer to identify patients with actionable changes in their tumors that could be treated with currently available therapies.

"Our data highlight just how difficult it is to do this sort of trial in a poor-prognosis cancer like pancreatic cancer," said Lorraine Chantrill, MBBS, FRACP, medical oncology staff specialist at Macarthur Cancer Therapy Centre in Campbelltown Hospital, and a researcher at The Kinghorn Cancer Centre, Garvan Institute of Medical Research, both in Australia. "We know that, unfortunately, only about 15 percent of the population had molecular targets eligible for this type of treatment and that it has been very difficult to do the molecular analysis quickly enough before patients get too sick to be treated."

Initially, the single-arm trial screened patients for three molecular targets: HER2 amplification, indicating treatment with trastuzumab/gemcitabine; KRAS wild-type, indicating treatment with erlotinib/gemcitabine; and DNA damage repair pathway defects, indicating treatment with platinum-based chemotherapy. While patients waited for the molecular analysis results, they were permitted to start standard-of-care chemotherapy treatment.

Patients in the initial cohort of the trial underwent disease resection, and 70 percent of patients eventually had disease recurrence. The researchers began collecting tissue for analysis in 2009; however, by the time the first trial site opened in April 2013, only eight patients with eligible molecular targets remained alive.

The researchers altered the trial design to conduct real-time screening for mutations in patients diagnosed with untreated metastatic disease. The screened mutations were expanded to include KRAS, BRCA1, BRCA2, PALB2, and ATM.

To date, the researchers have screened 93 tumors in 18 months and have found 22 patients with relevant molecular targets. The average time from biopsy to delivery of the molecular results was 21 days. "We have found that a non-randomized trial is more appealing to patients in this situation," Chantrill said.

"It is important for the public to know how hard it is to put into practice molecularly guided treatment within the constraints of our health service delivery," Chantrill added. "We hope that our work will help others who are planning similar studies." Senior author of the study, Andrew Biankin, MBBS, PhD, director of the Wolfson Wohl Cancer Research Centre in the University of Glasgow, United Kingdom, said, "It highlights how current healthcare systems are not well-aligned for a more personalized approach to therapy. Lessons learnt here could inform

appropriate changes in healthcare systems to enable precision medicine in practice."

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