Targeting metabolism in pancreatic cancer

Targeting altered metabolism in cancer is an intriguing concept. The Warburg effect—the observation that cancer cells use energy from glucose even when there is enough oxygen (aerobic glycolysis)—has been almost forgotten for a long time. However, recently, studies on cancer cell-specific metabolism have uncovered many of the biochemical mechanisms underlying this shift in energy provision. Several drugs have been developed that target altered metabolic pathways in cancer. Among these, CPI-613—an agent that inhibits cancer-specific mitochondrial energy metabolism—has recently gained attention and has been shown to be well tolerated and effective in various cancers. In The Lancet Oncology, Angela Alistar and colleagues report the findings of their a phase 1 study to establish a maximum tolerated dose of CPI-613 in patients with metastatic pancreatic cancer. The researchers not only postulated that CPI-613 would have few adverse events and that targeting tumour cell mitochondrial metabolism would exert anti-tumour effects, but that there would be synergy of CPI-613 with modified FOLFIRINOX chemotherapy.

Alistair and colleagues reported that this treatment combination was well tolerated at a maximum tolerated dose of 500 mg/m². The number of serious adverse events was low and, when present, events were clinically manageable. The investigators recorded no deaths due to adverse events; however, grade 3-4 adverse events are manageable. The investigators recorded no deaths due to adverse events; however, grade 3–4 adverse events were quite common. Thus, it can be concluded that the addition of CPI-613 is a reasonable strategy that does not impose too great a risk for patients with a good performance status (Eastern Cooperative Oncology Group performance status of 0–1 was an inclusion criterion in the study). Although activity was not a primary endpoint in the phase 1 study, the data suggest that the addition of CPU-613 to mFOLFIRINOX does not shorten progression-free survival (median progression-free survival was 11.5 months [95% CI 133–560]) and has encouraging effects on the numbers of patients responding to treatment (11 [61%] of 18 patients given the maximum tolerated dose achieved a partial or complete response). Furthermore, a comparison with a contemporary cohort of patients with metastatic pancreatic cancer given mFOLFIRINOX plus CPI-613 at the researchers’ institution showed a better survival of the combination treatment group of patients. However, this is a phase 1 study that has not been designed to show efficacy of the addition of CPI-613 to mFOLFIRINOX, and therefore these results need to be interpreted with caution.

As researchers have learned from testing small molecules and antibodies that target altered oncogenic signalling in pancreatic cancer, encouraging results from phase 1 studies have (almost) never been translated to clinically significant survival benefits in phase 3 trials. Actually, only polychemotherapy regimens have recently shown relevant efficacy in their respective large randomised trials (eg, FOLFIRINOX and gemcitabine plus abraxane). This situation also holds true in the adjuvant setting, where the most substantial progress has been made by combining gemcitabine with capcitabine, as recently shown the ESPAC-4 trial. However, when looking into the details of Alistar and colleagues’ study, many things can be learned. First, the investigators’ hypothesis that there might be synergy with mFOLFIRINOX could well be true in a subset of patients, as shown by the genetic makeup of the responders’ tumours. None of these patients had a SMAD4 mutation, but members of the mucin gene family were often mutated. As stated by the researchers in their supplementary web appendix, TGFβ-regulated, SMAD3/4-transcribed MUC gene activity “may result in a vulnerability to the combination therapy targeting genome and mitochondria-associated metabolism”. These results hold the promise of more individualised treatment in which CPI-613 could be added to standard mFOLFIRINOX treatment in subgroups of patients with a particular genetic makeup of the tumour. The researchers’ findings also indicated that serum carbohydrate antigen 19-9 (CA19-9) was a reliable biomarker for tumour response in their patient cohort. More translational research and more individualised, complex clinical trials will be needed to expand such findings by establishing even better biomarkers of response and resistance. In this respect, it will be necessary to study in more detail which patients will respond to an addition of a particular small molecule to chemotherapy and how response or resistance can be measured in real time rather than after completion of many cycles of a particular treatment regimen.
The phase 3 trial that Alistar and colleagues have designed and that is scheduled to be initiated shortly might provide interesting information about the efficacy of CPI-613 addition in a large cohort of patients with metastatic pancreatic cancer. However, irrespective of the results of this upcoming study, targeting cancer-specific metabolism using different drugs for different patients holds great promise for improving survival in this devastating disease.

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We declare no competing interests.