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Commentary

A PARP inhibitor in pancreatic cancer: Enhancement anti-tumour activity of chemoradiation therapy against pancreatic cancer?

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Pancraetic cancer is a disease with one of the worst prognoses, with the 5-year survival rate of patients diagnosed as having pancreatic cancer remaining at a dismal 5% to 10% [1]. Since it is difficult to diagnose pancreatic cancer at an early stage, 70%–80% patients with pancreatic cancer already have unresectable disease, including locally advanced or distant metastatic disease, at diagnosis. Chemoradiotherapy and chemotherapy are recognized as standards of care for unresectable locally advanced disease. A large phase III trial comparing chemoradiation therapy with chemotherapy, the LAP-07, recently failed to show any survival benefits of chemoradiation therapy over chemotherapy [2]. However, chemoradiation therapy may be expected to yield longer survival in patients with locally advanced pancreatic cancer, and various new treatments methods have been attempted.

Germline BRCA1/2 mutation is one of the factors involved in the pathogenesis, not only of breast and ovarian cancers, but also of pancreatic cancer, and the reported odds ratio of pancreatic cancer in patients with BRCA mutation is 2.13 to 2.55 [3]. Furthermore, there are also some reported differences in the sensitivity to chemotherapy, such as to regimens including platinum and/or poly (ADP-ribose) polymerase (PARP) inhibitors, between pancreatic cancers with and without BRCA mutation. BRCA1 and 2 play important roles in the repair of double-stranded DNA breaks. On the other hand, PARP is a protein that helps in the repair of single-strand breaks. PARP inhibitors target defective DNA repair in cancers with BRCA1/2 mutations by blocking the repair of single-strand breaks, leaving the double-strand breaks, thereby causing the death of the BRCA1/2-mutant cancer cells. Veliparib is an oral PARP-1/2 inhibitor and has been tried as monotherapy or in combination with a platinum-containing regimen [4,5]. Veliparib monotherapy exhibited modest activity against pancreatic cancer with BRCA1/2 mutation, yielding no case of confirmed response and a stable disease rate of 25% [4]. On the other hand, combined use of veliparib with gemcitabine plus cisplatin showed promising activity, with a response rate of 77.8% and median overall survival of 23.3 months in the limited cohort of patients with BRCA mutations in a phase I study [5]. A double-strand break is considered one of the most cytotoxic types of DNA damage, and homology-directed repair is one of pathways to repair a double-strand break. Mutations in several homology-directed repair genes, including not only BRCA1/2 mutation but also PALB2, RAD51C, RAD51D, PTEN, and ATM, which are associated with cancer developments such as beast, ovary, prostate, pancreas, and other cancers. Cancer cells with those mutations due to defects in DNA repair are sensitive to platinum-based chemotherapy to interfere with DNA replication. Thus, combination PARP inhibitor with platinum containing chemotherapy would be more effective to those cancers with BRCA1/2 mutation.

Tuli and coworkers [6] conducted a phase I study in which they compared chemoradiation therapy using veliparib in combination with gemcitabine and radiotherapy in patients with locally advanced pancreatic cancer. The authors previously published preclinical observations on the radiosensitising effect of veliparib both *in vitro* and *in vivo*. Based on their observations, it was considered that veliparib with radiation significantly enhanced the tumour response, resulting in dose-dependent feedback up-regulation of PARP and p-ATM, suggestive of increased DNA damage [7]. Chemoradiation therapy remains standard of care for locally advanced pancreatic cancer, and more advancements in the treatment techniques are required to enhance its efficacy. In this phase I study, the feasibility of combining veliparib with chemoradiation was demonstrated, but the efficacy was moderate, with median overall survival of 14.6 months and a partial response rate of 3%, yet with a disease control rate of 97% in a population unselected by up front chemotherapy.

Some issues should be considered to improve the treatment efficacy of a PARP inhibitor administered in combination with chemoradiation. PARP inhibitors are known to be relatively effective against cancers with BRCA mutations. Although the incidence of BRAC1/2 mutation is relatively low, being only up to 10% in patients with pancreatic cancer [8], candidates for treatment with a PARP inhibitor in combination with chemoradiation should be limited to those patients with germline BRCA1/2 mutations. While gemcitabine or an oral fluoropyrimidine, such as capecitabine, is usually used in concurrent chemotherapy in combination with radiotherapy, the dose of gemcitabine or radiation often has to be reduced due to toxicity. A randomized controlled trial comparing gemcitabine with capecitabine in chemoradiation therapy demonstrated that a capecitabine-based regimen might be preferable to a gemcitabine-based regimen for treating locally advanced pancreatic cancer, although the gemcitabine dose of (300 mg/m(2) once per week) was lower than what is typically used concurrent with radiation [9]. In the phase I study, the MTDs of gemcitabine and veliparib were investigated, with the radiation dose fixed at 36 Gy. The MTD of gemcitabine

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was determined to be 400 mg/m^2, much lower than the usually used dose of this drug of 1000 mg/m^2. Capecitabine could be given in combination with 50.4 Gy of standard-dose radiation, because capecitabine has the same antimetabolite activity as gemcitabine. Furthermore, cisplatin, a DNA-damaging agent, may enhance the activity in this treatment strategy of a PARP inhibitor administered in combination with chemoradiation.

Chemotherapy alone, such as with FOLFIRINOX or gemcitabine plus nab-paclitaxel, are commonly used for unresectable pancreatic cancer patients, including those with locally advanced disease. The reported median overall survival in patients treated with FOLFRIINOX was 18.5 months in a Japanese prospective observational study [10]. To date, no large randomized controlled trial has demonstrated the survival benefit of chemoradiation therapy over chemotherapy alone. It is required to demonstrate the superiority of chemoradiation therapy over chemotherapy alone from the point of view of the risk-benefit balance. To establish the most effective standard treatment for locally advanced pancreatic cancer, a large randomized controlled trial comparing chemotherapy and chemoradiotherapy may finally be required. On the other hand, use of a biomarker-based strategy, such as administration of a PARP inhibitor in combination with other strategies may be another way to establish the standard of care in specific populations, such as patients with BRAC1/2 mutation.

Disclosure

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