Long-term response to olaparib in a patient with metastatic pancreatic cancer associated with hereditary breast and ovarian cancer syndrome

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Abstract

BRCA mutations are associated with an increased risk of pancreatic cancer (PC). Olaparib, an oral poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor, has been approved for the treatment of metastatic PC with a germline BRCA mutation. In this report, we present the case of a metastatic PC harboring a germline BRCA2 mutation, and the daughter of the patient, who had bilateral breast cancers harboring the same germline mutation, suggesting that the PC was associated with hereditary breast and ovarian cancer syndrome. Although PC is an aggressive disease and has poor prognosis, olaparib was administered as maintenance therapy following modified FOLFIRINOX, providing clinical benefits for >12 months.

INTRODUCTION

Pancreatic cancer (PC) is a highly lethal malignancy that is fatal for more than 90% of patients, with approximately 70% succumbing to extensive metastatic disease and the remaining 30% dying from locally destructive PC [1]. Smoking, obesity and diabetes are all risk factors for PC, and genetic factors account for 5–10% of PC cases. The majority of familial PCs are caused by hereditary breast and ovarian cancer (HBOC) syndrome, which is caused by germline mutations in the BRCA1/2, with BRCA2 mutations being the most common genetic alteration [2].

First-line systemic chemotherapy for metastatic pancreatic adenocarcinoma is administered based on performance status, the presence of germline or somatic mutations in a homologous recombination repair (HRR) deficiency-associated gene, comorbidity, serum bilirubin level and histological grade. If an HRR deficiency-associated gene mutation is present, FOLFIRINOX (leucovorin plus short-term infusion of fluorouracil plus oxaliplatin and irinotecan) or dose-modified FOLFIRINOX is administered [3]. A poly(ADP-ribose)polymerase (PARP) inhibitor should be recommended for maintenance therapy rather than continued chemotherapy for patients with a germline BRCA pathogenic variant who have no disease progression after at least 16 weeks of initial platinum-based chemotherapy [4].

The BRCA1 and BRCA2 genes play a crucial role in directing high-fidelity homologous recombination (HR) repair [5]. In tumors with HR deficiency, such as those harboring BRCA1 and BRCA2 gene mutations, compensatory mechanisms fail to repair DNA damage, eventually accumulating damaged and unrepaired DNA and leading to cell death, a phenomenon known as synthetic lethality [5]. Inhibition of PARP has demonstrated marked efficacy against not only breast cancer but also PC with HR deficiency due to defects in BRCA1, BRCA2 or other pathway components [4].

Following the approval of olaparib, an oral PARP inhibitor, in Japan on 28 December 2020, physicians have been able to prescribe olaparib to patients with metastatic PC harboring a germline BRCA pathogenic variant. In this report, we present a case of metastatic PC harboring a germline BRCA2 mutation associated with HBOC syndrome and exhibiting a favorable response to olaparib maintenance therapy.

CASE REPORT

A 70-year-old man presented with lower back pain and weight loss. Thoracic and abdominal computed tomography revealed an enhancing 37 mm mass in the pancreatic body with a suspicious invasion of the portal vein and tumor embolism in the splenic vein, but no distant metastases or notable lymph node enlargement. Endoscopic ultrasound-guided fine-needle aspiration revealed Class V PC. The carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were elevated to 27.5 ng/ml (normal range up to 5 ng/ml) and 197 U/ml (normal range up to 37 U/ml), respectively. In November 2020, he was diagnosed with PC Stage IIA (T3N0M0) (Fig. 1a).
His brother had gastric and prostatic cancers, and his sister had bilateral breast cancer. Five months before the diagnosis, his 38-year-old daughter was diagnosed with synchronous bilateral breast cancer and underwent bilateral mastectomy and BRACAnalysis (Myriad Genetics), which revealed a BRCA2 variant (c.7666_7667dupAA) (Fig. 2). When he was diagnosed with PC, the gastroenterologist was unaware of his daughter’s BRCA2 variant. He received neoadjuvant chemotherapy consisting of two cycles of nab-paclitaxel and gemcitabine. During neoadjuvant chemotherapy, the gastroenterologist received information about the genetic variant from his daughter’s doctor. The effect of neoadjuvant therapy indicated a partial tumor response, with CEA and CA19-9 levels rapidly declining prior to surgery (Figs 1b and 3a). However, surgical resection was not completed because peritoneal dissemination was detected (i.e. Stage IV [T3N0M1]) immediately after the surgery started. Modified FOLFIRINOX (oxaliplatin [68 mg per square meter of body surface area], irinotecan [90 mg per square meter], leucovorin [200 mg per square meter] and fluorouracil [1500 mg per square meter] every 2 weeks) was then administered, and a BRACAnalysis revealed a BRCA2 variant (c.7666_7667dupAA). Three cycles of modified FOLFIRINOX were administered because of adverse events, such as anorexia, which did not allow the continuation of treatment till 16 weeks, the negligible effect of further dose reduction on the disease, and the fact that the patient strongly requested changing FOLFIRINOX administration. This led to the stabilization of the disease. Olaparib was then initiated as maintenance therapy, resulting in a continuous partial response over a 12 month treatment period, and CEA and CA19-9 levels gradually decreased over the next couple of months and remained within normal ranges (Fig. 3a and b). Two months after treatment, Grade 3 anemia was detected, and the olaparib dose was reduced to 300 mg based on the severity of the anemia (Fig. 3a). Grade 1 stomatitis was also detected. When the side effects alleviated, the dose was increased to 500 mg until they worsened again (Fig. 3a).
DISCUSSION

Pathogenic variants in the *BRCA1* and/or *BRCA2* genes are associated with an increased risk of not only ovarian and breast cancers, but also PC, with 4–7% of patients with PC harboring a germline *BRCA* mutation [6]. The *BRCA* genes encode proteins involved in the HR repair of double-strand DNA breaks [5]. *BRCA* pathogenic variants are sensitive to PARP inhibition via multiple mechanisms, including PARP trapping on DNA at sites of single-strand breaks, which cannot be repaired accurately in tumors with HR repair defects, resulting in synthetic lethality. Therefore, PARP inhibitors cause an accumulation of DNA damage in tumor cells with a deficiency in DNA damage repair, resulting in tumor cell death [7]. The PARP inhibitor olaparib has been shown to be clinically effective in patients with ovarian or breast cancer harboring a germline *BRCA* mutation [8, 9]. Additionally, in a Phase III POLO trial, patients with metastatic PC who had a germline *BRCA* mutation had not had progressive disease during platinum-based chemotherapy—of whom, more than 80% were receiving the FOLFIRINOX regimen—benefited from maintenance therapy with olaparib [4].

The majority of *BRCA2* mutations identified in PC were frameshifting indels and splice-site mutations, whereas single point mutations are uncommon [6]. In the present case, the pathogenic mutation c.7666_7667dupAA is located in coding exon 15 of the *BRCA2* gene, causing a translational frameshift with a predicted alternate stop codon (p.N2556Kfs*15). This mutation was identified in a Japanese PC cohort [10]. In addition to the clinical data presented in the literature, this alteration is expected to result in loss of function via premature protein truncation or nonsense-mediated mRNA decay.

Olaparib provided the patient with >12 months of partial response, while the median progression-free survival reached 7.4 months, with fatigue, nausea and anemia being the major adverse events, and the reported frequency of Grade 3 or higher anemia was 11% in the POLO trial. The patient reported herein had Grade 3 anemia, which was alleviated by lowering the olaparib dose. Olaparib is available in a tablet form, and no significant differences in the quality of life of patients have been reported between the olaparib group and placebo group in the POLO trial [4]. FOLFIRINOX, a standard of care for metastatic PC, is a cytotoxic chemotherapy that is administered in the form of an infusion. Furthermore, the safety profile of FOLFIRINOX is less favorable than that of gemcitabine even though FOLFIRINOX significantly reduces quality of life impairment in patients with metastatic PC compared with gemcitabine. It has been reported that approximately 30% of patients had disease progression during their first 4 months of treatment with FOLFIRINOX [9]. The patient reported in the present study received a dose-reduced modified FOLFIRINOX from the initial cycle because of the risk of severe adverse events. Therefore, if the patient continued the modified FOLFIRINOX, achieving 12 months of disease control would not have been possible. Moreover, the patient did not meet the criteria for olaparib therapy as he had received first-line platinum-based chemotherapy for only 8 weeks. However, it was an appropriate therapy in terms of the palliative treatment because the important goals in metastatic cancer therapy are a longer survival time, improvement of quality of life, and management of symptoms. Olaparib provided the patient with clinical benefits for >12 months and a better quality of life.

In the present report, the patient opted for a *BRACAnalysis* because a breast surgeon and a gastroenterologist were able to share information about his daughter’s *BRCA2* mutation on conversation, despite his remarkable family history of cancer. Therefore, along with clinician communication, it is critical that clinicians share genomic information on medical records or other systems that protect patients’ privacy and keep family histories up-to-date. Screening and early detection of cancer in this family with hereditary *BRCA2* mutation can save other members in the future. Because the use of *BRCA* testing for cancer screening and tailoring cancer treatment has increased in the mainstream oncology practice, it may be important to build a genetic information management system and method so that clinicians should standardize *BRCA* testing practices.

In conclusion, as a maintenance therapy, olaparib was associated with a good response in patients with HBOC syndrome and a germline *BRCA2*-mutated metastatic PC. Sharing genetic information
Figure 3. (a) The patient’s clinical course. CEA, CA19-9 and hemoglobin levels before and after olaparib administration. (b) A CT scan revealing the pancreatic body tumor before the olaparib administration in the left panel and the right panel showing the tumor after 12 months of the treatment. The arrow indicates the pancreatic body tumor.

CONFLICT OF INTEREST STATEMENT
No conflict of interest.

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The authors have no funding sources to report.

ETHICAL APPROVAL
Ethical approval was not required for this study in accordance with local or national guidelines.

CONSENT
The patient provided written informed consent for publication of this case, including images.

GUARANTOR
Ryoichi Matsunuma.

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