

CASE REPORT

Combined anti-PD1 immunotherapy for patient with advanced pancreatic cancer: A case report

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Abstract

Pancreatic cancer (PC) is a highly lethal malignancy with a dismal 5-year survival rate. The current treatment modalities for the treatment-associated toxicity of immunotherapy-based approaches are limited. Immunotherapy for PC was needed to be further investigated. This report illustrates the combined use of anti PD-1 immunotherapy with other therapeutic strategies for cancer pain. In this case, a patient with PC was treated with surgical resection, chemotherapy, molecular targeted medicine, and anti-PD1 immunotherapy. The survival period of the patient was more than 6 years since diagnosis. Finally, we will present our perspective on the future development of immunotherapy for PC. In a word, this case report sheds lights on information that would be helpful for more rigorous exploration of PC treatments.

Keywords: Pancreatic cancer; Immunotherapy; PD1

1. Background

Pancreatic cancer (PC) leads to an estimated 227,000 deaths per year worldwide^[1]. Only about 4% of patients can survive 5 years after diagnosis. Nowadays, surgical resection is the mainstay of the treatment for PC^[2]. However, 80–85% of patients are presented with advanced unresectable disease^[3]. Adjuvant treatment is recommended for individuals who undergo pancreatic resection with curative intent.

Chemotherapy is the mainstay of the treatment for individuals with advanced disease^[4]. Gemcitabine is standard for patients with advanced PC; it induces a partial response in a few people and can alleviate symptoms to some extent with advanced tumors.

Fractionated radiation therapy is typically delivered with fluorouracil or capecitabine, an oral fluoropyrimidine that acts as a radiosensitizer. Different types of radiation therapy, such as intensity-modulated radiation therapy and stereotactic body radiation therapy, enable dose escalation and sparing of healthy tissues that could improve tumor control with tolerable side effects, but these modalities need further assessment in prospective clinical trials^[5].

The most important pathways include those targeted for genetic and epigenetic alterations, that is, those that include protein products of KRAS, RB1 and CDKN2A, TP53, and SMAD4 and TGFB1 genes^[6]. Germline mutations in *BRCA2*, *PALB2*, *CDKN2A*, *STK11*, and *PRSS1* genes, and Lynch syndrome, are associated with a substantially increased risk of PC. In Phase III clinical trials, the combination of

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gemcitabine and the epidermal growth factor receptor (EGFR) inhibitor, erlotinib, which is a tyrosine kinase inhibitor of the catalytic domain of EGFR, was modestly superior to gemcitabine alone^[7]. The standard second-line treatment is non-existent in PC. Therefore, clinical trial of new agents for treating PC is important since it has a high mortality rate and therapeutic benefits of the currently available treatment methods are typically modest.

The approval of several PD-1/PD-L1 and CTLA-4 inhibitors in the recent years has radically transformed the treatment landscape in many cancer types and opened up a new field called immune-oncology as a new treatment approach against cancer^[8]. Despite major breakthrough, shortcomings of immune checkpoint inhibitors (ICI) have been observed.

Here, we present a case of a patient with PC who was treated with surgical resection, chemotherapy, molecular targeted medicine, and anti-PD1 immunotherapy. The level of CA 19-9 and tumor size of the patient were evaluated. The survival period of the patient was more than 6 years since the diagnosis of PC. At the end of the report, we include our perspective on the future development of immunotherapy for PC.

2. Case presentation

In October 2014, a 66-year-old man was admitted to our hospital. At the time of admission to the hospital, the patient had an elevated level of CA 19-9, and positron emission tomography/computed tomography (PET-CT) examination indicated tumor at pancreatic body and tail. Intra-operative exploration found a small amount of ascites in the abdominal cavity, a mass of 3 × 2 × 2 cm in size was detected near the splenic portal in the tail of the pancreas, which invaded the lower pole of the spleen and the perirenal fat sac, and no enlarged lymph nodes were detected in the abdominal cavity. Therefore, radical treatment of PC and splenectomy was performed. Post-operative pathologic examination indicated the presence of a mucinous adenocarcinoma at the pancreatic body and tail, which was manifested as medium differentiation, invasion of peripancreatic fat, and one tumor deposit. Pathologic staging of the tumor was pT2N0M0. Post-operative CA 19-9 level dropped to normal. After six cycles of gemcitabine and S-1 adjuvant chemotherapy, the regimen was replaced by single drug S-1 (two pills in the morning and two pills at night) for the purpose of maintenance treatment, which was continued until January 2018, during which no obvious abnormality was found in abdominal CT review for 6 months. In January 2018, we found that a new mass developed in the periumbilical scar. The mass was resected in the hospital. Post-operative pathologic examination showed that the mass was a mucinous adenocarcinoma.

In addition, findings from PET-CT suggested peritoneal metastasis in the patient. As shown as [Figure 1A](#), albumin-bound paclitaxel and gemcitabine were administered for six cycles starting February 2018, and the last cycle was performed in June 2018. During chemotherapy, heart failure was detected once in the patient, but the condition improved after treatment. The patient condition was hence classified as stable disease, and the drug was discontinued for 2 months.

In August 2018, the patient's carcinoembryonic antigen (CEA) and CA 19-9 levels were 14 ng/ml and 25.8 ng/ml, respectively. Abdominopelvic CT showed new nodules in the right paracolic sulcus as well as medial descending colon, indicating a possible severe metastasis. Pelvic effusion and multiple lymph nodes in the abdominal cavity ([Figure 1B](#)) were roughly the same as before. The albumin-bound paclitaxel and gemcitabine were continued for four cycles, during which CEA level gradually increased to 31.9 ng/ml. After four cycles, the right paracolic groove, the medial descending colon, the greater omentum, and the retroperitoneal left subphrenic nodules in the abdominal cavity appeared larger in size than before. The bladder and rectum were also enlarged. In view of the above, the disease had become progressive.

In October 2018, the CEA and CA 19-9 levels were 52.6 ng/ml and 48.1 ng/ml, respectively. The patient started FOLFIRINOX chemotherapy regimen for four cycles, and the treatment tolerance was acceptable. A review of treatment efficacy after four cycles showed that the disease had become stable, and the CEA and CA 19-9 levels were 20.9 ng/ml and 48.9 ng/ml, respectively. FOUNDATION ONE gene sequencing was used to test for microsatellite stability, tumor mutation burden 18Muts/Mb, and BRAF T599_V600insT mutation. Immunohistochemical findings showed that the patient was negative for PD-L1 and PD-1.

In December 2018, FOLFIRINOX+KEYTRUDA was performed for a total of four cycles, and reexamination in February 2019 ([Figure 1C](#)) showed that multiple intraperitoneal implantation metastasis was diminished, and at the same time, the CEA and CA 19-9 levels were 9.73 ng/ml and 49 ng/ml, respectively. The efficacy of the treatment on partial remission was evaluated. KEYTRUDA treatment was performed for 4 times from February 2019 to May 2019. In May 2019, the drug was replaced with anlotinib (12 mg d1 – 14 q21d) + keytruda for a total of four cycles. Due to hand-foot syndrome, cough, and elevated blood pressure, the dosage of anlotinib was reduced to 8 mg d1 – 14d q21d after two cycles. Immunotherapy was continued to be used the patient, who attended the follow-up sessions and periodic review. The treatment had improved cancer pain and stabilized the patient's condition and the disease had not progressed. Despite that, the patient still needs treatment and periodical follow-up.

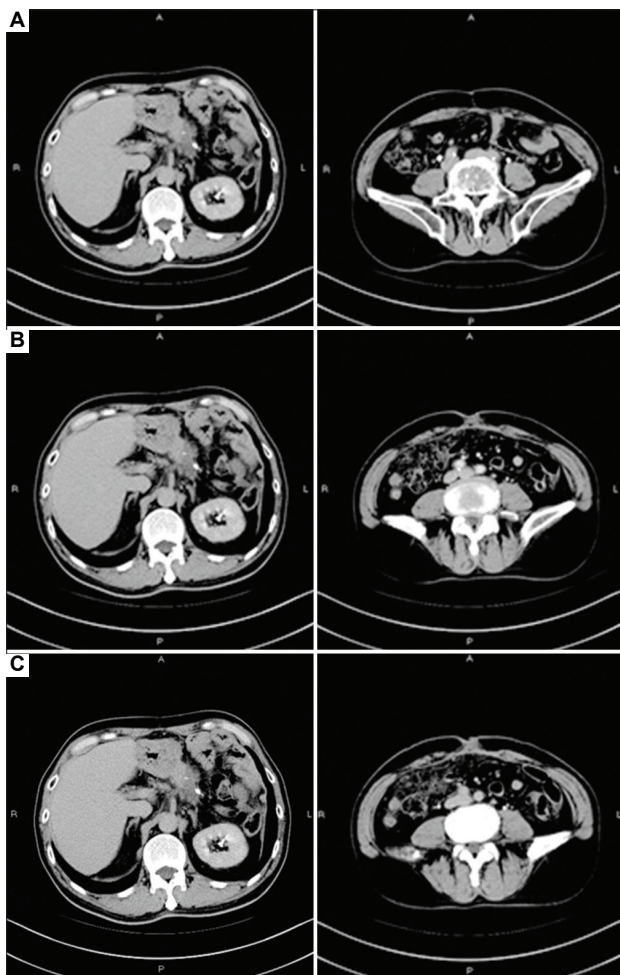


Figure 1. Imaging results. (A) Post-operative and peritoneal metastasis in February 2018. (B) Disease progression and local recurrence in August 2018. New nodules in the right paracolic sulcus as well as medial descending colon, indicating a possible severe metastasis. Pelvic effusion and multiple lymph nodes in the abdominal cavity were roughly the same as before. (C) In February 2019, intraperitoneal implantation metastasis diminished after immunotherapy was used.

3. Discussion

PC is a highly lethal malignancy with a dismal 5-year survival rate^[9]. Poor tumor penetration and highly immunosuppressive tumor microenvironment are two major factors that limit the therapeutic efficacy of the treatment for PC. Only about 4% of patients with PC can survive 5 years after diagnosis. This is due to its asymptomatic nature, lack of reliable biomarkers, poor resectability, early metastasis, and high recurrence rate^[10]. Surgical resection is the only widely accepted treatment modality for PC. Furthermore, 80–85% of patients are presented with advanced unresectable disease. Chemotherapy can be used in those with adequate performance status, but it is not effective for those with poor performance status^[11].

Fortunately, immunotherapy has gradually transformed the therapeutic landscape for various solid tumors, such as renal cell cancer, lung cancer, melanoma, and others. In the field of immunotherapy, many clinical trials are being performed to test the efficacy of immunotherapy in PC, for example, the application of adoptive cell transfer, cancer vaccines, ICI, and combinations with molecular targeted agents or chemoradiotherapy. It is reported that PD-L1 expression is a prognostic response to immunotherapy in PC, so anti-PD-1 immunotherapy holds promise in the future treatment of PC. In addition, the combination of cytotoxic drugs and immunotherapy seems to result in a synergistic effect^[12].

In this case report, we present our experiences in treating a PC patient using surgical resection, chemotherapy, molecular targeted medicine, and anti-PD1 immunotherapy. The combined treatment modalities turned out to be successful in extending the patient's survival time to more than 6 years since diagnosis. That being said, the application of immunotherapy in combination with different therapeutic strategies might offer a favorable treatment option for PC patients.

However, the current treatment modalities for the treatment-associated toxicity of immunotherapy-based approaches are limited. Even though immunotherapy can significantly improve cancer pain and provide an overall favorable clinical and survival benefit, the use of immunotherapy for PC still needs to be further investigated^[13].

4. Conclusion

In this case report, we present our experiences in treating a PC patient using surgical resection, chemotherapy, molecular targeted medicine, and anti-PD1 immunotherapy. The survival period of the patient was successfully extended to more than 6 years since diagnosis of PC. The combined treatments also contributed to a significant decrease in CA 19-9 level. In summary, our findings would be very helpful for the future studies that attempt to explore PC treatments in-depth.

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Conflict of interest

The authors report no conflict of interest.

Author contributions

Conceptualization: Hongyan Li

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Ethics approval and consent to participate

This research was approved by the Ethics Committee of The Xuan Wu Hospital (No. 2020027). The patient described in this study has given his informed consent to participate in this study.

Consent for publication

Informed consent has been obtained from the patient for publication of this case report.

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