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Case Report

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Survival Benefit of Pembrolizumab for Patients With Pancreatic Adenocarcinoma: A Case Series

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with 5-year survival rate of 10%. Evidence about pembrolizumab usage for PDAC is limited even though it is Food and Drug Administration (FDA)-approved for treatment of advanced pancreatic cancer with deficient mismatch repair expression (dMMR) or high tumor mutational burden (TMB) where as there is limited evidence for programmed death-ligand 1 (PD-L1)-positive PDACs. We present three patients with different stages of advanced PDAC treated with pembrolizumab as single maintenance therapy or combination with other therapy. Case 1 is a patient with borderline resectable PDAC, treated with neoadjuvant chemotherapy and surgical resection, followed with pembrolizumab as maintenance therapy with no progression for 4 years after test showed patient was dMMR positive. Case 2 is a patient who was found to have locally advanced PDAC, treated with neoadjuvant chemotherapy and surgical resection followed by multiple line of treatment with programmed cell death-1 (*PD-1*) and breast cancer gene 2 (*BRCA2*)-positive status treated with pembrolizumab and olaparib maintenance without any evidence of progression for more than 3 years. Case 3 is a patient with metastatic PDAC with *PD-1* and *BRCA2*-positive status initially treated with FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) and gemcitabine plus nab-paclitaxel switched to irinotecan liposomal, at the same time was started on maintenance pembrolizumab and olaparib with no progression on computed tomography (CT) surveillance for 8 months. For patient with different stages of PDAC with dMMR mutation or *PD-1* expression, pembrolizumab should be explored more as maintenance therapy for patients with surgical operable PDAC to decrease recurrence, or as a combination with targeted therapy or chemotherapy to prolong survival in patients with advanced PDAC.

Keywords: Pancreatic ductal adenocarcinoma; Pembrolizumab; Anti-programmed death-1 inhibitor; Survival

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with a 5-year overall survival of approximately 10% [1, 2]. Treatment options include surgical resection with adjuvant chemotherapy; systemic chemotherapy combinations such as FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin), gemcitabine plus nab-paclitaxel as the mainstay of treatment for patients with advanced disease [3, 4]. Despite improvements in surgery and chemotherapy, PDAC remains highly chemo-resistant and as a result survival benefit of available therapies is moderate with poor overall outcome.

Pembrolizumab is an anti- programmed cell death-1 (PD-1) immune checkpoint inhibitor, which is Food and Drug Administration (FDA)-approved for the treatment of patients with advanced PDAC whose tumors are deficient mismatch repair expression (dMMR) with high microsatellite instability (MSI-H) or high tumor mutational burden (TMB), and have shown progression on prior treatment in whom there is no satisfactory alternative treatment options [3, 4]. There have been several trials on the use of pembrolizumab or other checkpoint inhibitor for PDACs with very narrow recommendation for use in PDAC. With above approved indications, the role of pembrolizumab for PDAC is very limited considering low incidence of dMMR in PDAC with ranging from 0.8% to 2% and rapid clinical decline of patients [5, 6]. In our case series, we are discussing three patients with different stages PDAC who have been on pembrolizumab as single maintenance therapy or combination with other therapy for 1 - 4 years, providing evidence of usage options of pembrolizumab in different stages of PDAC with additional survival benefit for patients.

Case Reports

Case 1

Patient is a 51-year-old female presented to our hospital 5 years ago with several weeks of abdominal pain, dark colored urine, jaundice, and anemia. Ultrasound (US) and computed tomography (CT) revealed a 6-cm cystic/solid mass in head of pancreas. Endoscopic ultrasound (EUS) confirmed a mass in the head of the pancreas which also involved the second portion of the duodenum. There was no adjacent lymphadenopathy. Subsequent biopsy revealed PDAC. Magnetic resonance imaging (MRI) of

Table 1. Summary of Three Cases

Case series	Case 1	Case 2	Case 3
Age on diagnosis (years)	51	63	35
Clinical staging	Borderline resectable	Initially locally advanced and recurrence with metastatic	Metastatic
MMR status	Deficient MMR expression	Intact MMR expression	Intact MMR expression
Tumor mutational burden status			
PD-L1 status	Not tested	*PD-L1* positive	*PD-L1* positive
Treatment	Neoadjuvant chemotherapy and surgical resection	Neoadjuvant chemotherapy and surgical resection followed by chemoradiation	Three different regiments of chemotherapy due to progression
Use of pembrolizumab	Single maintenance therapy	Combine with olaparib as maintenance therapy	Combine with chemotherapy and olaparib
Follow-up	4 years	3 years	8 months

MMR: mismatch repair expression; *PD-L1*: programmed death-ligand 1.

the abdomen verified a 6.3-cm pancreatic mass in head of pancreas and there was no evidence of distant metastatic disease.

The patient underwent percutaneous biliary drainage for relief of biliary obstruction. Decision was made to treat patients with preoperative neoadjuvant chemotherapy of four cycles of FOLFIRINOX and followed by surgical resection. After two cycles of FOLFIRINOX a repeat CT scan was performed which did not show any change in the size of the pancreatic head mass and then next two cycles were completed. The patient was subsequently treated with gemcitabine based chemoradiation with follow-up CT scan showing pancreatic mass with pancreatic duct dilation and no evidence of distant metastatic disease. Then patient underwent pylorus preserving pancreaticoduodenectomy. Final pathology revealed 5-cm mass involving duodenum and pancreas which was consistent with high-grade poorly differentiated adenocarcinoma. The tumor extended focally involving the ampulla. Surgical margins were negative and four of seven lymph nodes were found to be positive for microscopic extension. The pathologic stage was determined to be T4N2M0.

Immunohistochemistry test showed the tumor to be dMMR with *MLH1* and *PMS2* loss of expression. After a prolonged postoperative course of 10 months, patient was started on a clinical trial with pembrolizumab 4 years ago. She has tolerated it well with only night sweats as an chronic issue. The patient was clinically improved with weight gain and increased oral intake. The repeated imaging showed no significant internal change with no evidence of recurrence over past 4 years. Ongoing maintenance therapy with pembrolizumab has been tolerated well and patient remains with a good performance status (Table 1).

Case 2

Patient is a 63-year-old male who presented 4 years ago with 40-lb weight loss, right upper quadrant abdominal pain and jaundice. Magnetic resonance cholangiopancreatography (MRCP) showed 4.5 × 4.9 cm pancreatic head mass with biliary obstruction, partial encasement of the superior mesenteric vein (SMV) and abutment of superior mesenteric artery. CT scan of the chest, abdomen and pelvis revealed a pancreatic mass with biliary dilation but no metastatic disease. EUS showed a 4.5-cm mass in the pancreatic head invading duodenal wall, there was a partial duodenal obstruction, the tumor abutted SMV and inferior vena cava (IVC) but there was not any SMV involvement. Fine needle aspirate cytology revealed malignant cells which was consistent with adenocarcinoma.

The patient underwent percutaneous placement of an internal/external biliary catheter with resultant decrease of abdomen pain and resolution of jaundice. Considering patient had locally advanced PDAC, he was started on neoadjuvant chemotherapy FOLFIRINOX and completed eight cycles. Repeat CT scan revealed that pancreatic mass had decreased in size and the ductal dilatation was unchanged. Then he received chemoradiation with capecitabine. Repeat CT scan showed that the pancreatic head mass was essentially unchanged, and no new lesions were present. The patient underwent pancreaticoduodenectomy and portal vein venorrhaphy with an uneventful postoperative course. Final pathology revealed infiltrating ductal adenocarcinoma with extension into the peripancreatic soft tissue with a focal adenocarcinoma within the muscular wall of the duodenum. No lymphovascular invasion was seen. The final pathologic stage was T3N0M0.

The tumor has a normal MSI but was found have programmed death-ligand 1 (PD-L1); tumor proportion score (TPS) was 1%. Germline breast cancer gene 2 (*BRCA2*) mutation was also positive. Postoperatively, the patient received four cycles of FOLFIRINOX and then underwent surveillance with blood testing and repeated CT scan.

Half a year later cancer antigen 19-9 (CA 19-9) was noted to be elevated, and positron emission tomography-computed tomography (PET-CT) scan revealed focal uptake in the pancreatic body surrounding the stent and borderline prominent mediastinal lymph nodes. MRI did not reveal recurring mass in pancreatic body. CA 19-9 continued to increase, and repeated PET-CT showed that the size of the hypermetabolic lesion had increased. The patient was thought to have recurrence of PDAC, and he was started on gemcitabine plus nab-paclitaxel and completed 11 cycles. Repeat MRI of the abdomen showed

a recurrence in the right hepatic lobe, and it was treated with irradiation therapy. Subsequently, the patient was started on pembrolizumab and then olaparib was added 5 months later, and both has been continued over past 3 years. Patient is doing well with good appetite, a good performance status and no significant adverse effect. Repeat imaging showed the stable disease with no evidence of progression (Table 1).

Case 3

Patient is a 35-year-old male who initially presented 2 years ago with complaints of generalized weakness and nausea for 1 month. He also had jaundice and mild abdominal pain. CT scan showed a 1.1-cm hypoattenuated lesion in the uncinate process of the pancreas, moderate intrahepatic and extrahepatic dilatation with distention of the gallbladder and the common bile dule. Liver biopsy confirmed PDAC.

The patient was started on chemotherapy FOLFIRINOX and completed six cycles. On repeated CT scan of the chest/abdomen/pelvis, multiple new lesions were found in the liver which was thought metastatic disease. Pathology showed MSI intact, and Foundation Medicine showed low TMB, MSI stable, *BRCA2* and *KRAS* mutation positive, genetic test showed germline *BRCA2* positive. For his metastatic PDAC, the patient was started on gemcitabine plus nab-paclitaxel and he completed 13 cycles. Repeated CT scan showed a new 1-cm lesion in the pancreatic head with numerous hypodense liver masses and some increase in size of the mass.

Immunohistochemistry for PD-L1 showed combined positive score 10-20% confirming with PDL1-positive status. The patient was then started on pembrolizumab and olaparib. Repeat CT scan 3 months later showed mild increase in size of the liver lesions and interval increase in size of pancreatic head malignancy. Then chemotherapy irinotecan liposomal was started and pembrolizumab and olaparib were continued. Repeated CT 3 months later showed the size of the pancreatic head mass to be unchanged and there was mild interval improvement in hepatic metastatic disease.

The patient has been stable with no progression on imaging while on combination of irinotecan liposomal, pembrolizumab and olaparib over past 8 months. He is clinically doing well with good performance status, a good appetite and no abdominal pain, nausea or vomiting. He had mild diarrhea which was controlled with Imodium (Table 1).

Discussion

The 5-year survival rate at the time of diagnosis is 10% in the USA. Approximately 80-85% of patients present with either inoperable or metastatic disease [1, 2]. Even for the patients with localized operable tumors, the prognosis remains poor with only 20% surviving 5 years following surgery [4]. Despite the development in surgical techniques and traditional chemotherapies, only modest survival benefits have been seen.

Pembrolizumab is a humanized immunoglobulin G4 monoclonal antibody which primary works by increasing immune-mediated tumor destruction. Pembrolizumab binds with inhibitory immune checkpoint receptor PD-1 expressed on lymphocytes inhibiting binding of its ligands PD-L1 and PD-L2, thereby allowing reactivation of T-cell-mediated destruction of malignant cells [7]. dMMR tumors have 10 - 100 times more mutations than proficient MMR tumors, which makes them particularly susceptible to mutations in repetitive DNA sequences leading to high level of microsatellite instability (MSI-H) [5, 6]. The genes that govern mismatch repair include *MLH1*, *MSH2*, *MSH6*, and *PMS2* [6]. In our first case, there was *MLH1* and *PMS2* loss of expression which indicated dMMR status. Cells from mismatch repair-deficient tumor can express PD-L1 on their membrane and these immune cells can display unregulated checkpoint proteins including PD-1 as in cases 2 and 3 [6]. MSI-H/dMMR and expression of *PD-L1* can be used as biomarker as a potential predictor of response to pembrolizumab treatment [5]. Each patient with PDAC, irrespective of stage, should be tested for these related biomarkers.

There are several clinical trials studying the effect of pembrolizumab on PDAC. KEYNOTE-158 is a nonrandomized, open-label multisite phase II study that enrolled patients with MSI-H/dMMR advanced non-colorectal cancer who experienced treatment failure and then received pembrolizumab for 2 years. Totally, 233 patients with 27 tumor types were enrolled. They enrolled 22 patients with PDAC, whose median progress-free survival was 2.1 months and median overall survival was 4 months [8]. In KEYNOTE-028 trial, a nonrandomized phase Ib trial, they enrolled patients with *PD-L1* positive advanced solid tumors receiving pembrolizumab for 2 years. It was shown that higher response rates and longer progress-free survival were demonstrated in tumors with *PD-L1* expression and tumor mutation burden [8]. These trials gave us some evidence that pembrolizumab can be used for the treatment of patients with advanced PDAC, but participants progression-free survival was not as exceptional as our case series. In addition, their follow-up time is limited, but in our case series, we have followed the patients for 4 to 5 years which shows pembrolizumab can be used for long term with great response effect and good tolerance.

The guideline of management of different stages of PDAC is based on the preoperative stage, and pembrolizumab can play different roles in various stages of PDAC. In case 1, the patient was considered to have a tumor which was borderline operable. Patient underwent preoperative chemotherapy, chemoradiotherapy, and then surgical resection as recommended in guideline [3]. However, here is no consensus for postoperative adjuvant treatment for operable or borderline operable PDAC. There is also no consensus for maintenance therapy which can decrease the risk of recurrence. Their 5-year survival rate is reported at 20% [4]. Our patient has been on pembrolizumab and has been progress free for more than 5 years. This suggests that pembrolizumab may have reasonable effect and should be explored more as postoperative maintenance therapy for localized or regional PDAC in a patient who has dMMR/MSI-H or *PD-L1* expression.

Apart from use as a single agent for maintenance therapy, pembrolizumab may also be combined with other targeted therapy or chemotherapy to prolong survival. In case 2, the patient had recurrence of PDAC after adjuvant chemotherapy. He had both *BRCA2* mutation and *PD-L1* expression, and he

was started on pembrolizumab and olaparib. Olaparib, a poly adenosine diphosphate-ribose polymerase (PARP) inhibitor improved median progress-free survival in patients with germline *BRCA1* or *BRCA2* mutations, who were not progressing after at least 16 weeks of first-line platinum-based chemotherapy [9]. In one of the recent reports, a patient with *BRCA1* mutation and high tumor mutation burden showed complete response to olaparib and pembrolizumab combination therapy [10]. Even in our study, patient has been doing well for more than 3 years without progression. The combination did not increase adverse effects but did seem to add to survival benefit.

In case 3, the patient had metastatic PDAC and had progression while on gemcitabine plus nab-paclitaxel. Since he had *BRCA2* mutation and *PD-1* expression, he was started on pembrolizumab and olaparib. In the NAPOLI-1 trial, patients with metastatic disease who had progressed on gemcitabine-based therapy were found to have an increased median overall survival with fluorouracil plus leucovorin with liposomal irinotecan compared with fluorouracil plus leucovorin (6.1 months vs. 4.2 months) [9]. But our patient was on irinotecan liposomal and was continued on pembrolizumab with a better progress-free survival than the trial participants. This case suggests another combination of chemotherapy and checkpoint inhibitors to be explored for PDAC.

Conclusions

PDAC is highly chemo-resistant tumor with very low tumor mutation burden with limited advancement in treatment. Our case series showed pembrolizumab has potential role in patients with varying stages of PDAC. Pembrolizumab use has been approved for dMMR/MSI-H tumors but there are very limited data on use for PDAC with *PDL-1* expression. One of the major limitations of our study is that this is a case series report without a control group or blinding needed to remove the bias, but it does raise an important point of need for more research for use of checkpoint inhibitor for PDACs. As the incidence of mismatch repair deficiency in PDAC has been reported to range 0.8% to 2% [7], its previous clinical trial data are not very convincing, and we need more clinical trials for different stages and involving different combinations to complete management guidelines.

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None to declare.

Conflict of Interest

None to declare.

Informed Consent

Written informed consents were obtained from the patients for publication of their individual details in this manuscript.

Author Contributions

Li Zhao took care of the patients and Patrick Lee supervised patient care. Li Zhao wrote the manuscript. Anthony Ricca and Vinit Singh reviewed and edited the manuscript. Patrick Lee edited the manuscript. All authors read and approved of the final manuscript.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

References

1. American Cancer Society. Cancer Facts & Figures 2020. Atlanta, GA: American Cancer Society, 2020.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.
3. NCCN guidelines Version 1. 2022 Pancreatic Adenocarcinoma. www.nccn.org.
4. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. Lancet. 2020;395(10242):2008-2020.
5. Bian J, Almhanna K. Pancreatic cancer and immune checkpoint inhibitors-still a long way to go. Transl Gastroenterol Hepatol. 2021;6:6.
6. Marabelle A, Le D, Ascierto PA, Di Giocomo AM, De Jesus-Acosta A, et al. Noncolorenal high microsatellite instability/Mismatch repair-deficient cancer: results from the phase II Keynote-158 study. Journal of Clinical Oncology. 2019;38:1-9.
7. Chi J, Patel R, Rehman H, Goyal S, Saif MW. Recent advances in immunotherapy for pancreatic cancer. J Cancer Metastasis Treat. 2020;6:43.
8. Ott PA, Bang YJ, Piha-Paul SA, Razak ARA, Bennouna J, Soria JC, Rugo HS, et al. T-cell-inflamed gene-expression profile, programmed death ligand 1 expression, and tumor mutational burden predict efficacy in patients treated with pembrolizumab across 20 cancers: KEYNOTE-028. J Clin Oncol. 2019;37(4):318-327.
9. Lellouche L, Palmieri LJ, Dermine S, Brezault C, Chaussade S, Coriat R. Systemic therapy in metastatic pancreatic adenocarcinoma: current practice and perspectives. Ther Adv Med Oncol. 2021;13:17588359211018539.
10. Lundy J, McKay O, Croagh D, Ganju V. Exceptional response to Olaparib and pembrolizumab for pancreatic adenocarcinoma with germline BRCA1 mutation and high tumor mutation burden: case report and literature review. JCO Precis Oncol. 2022;6:e2100437.