

Unexpected favorable outcome to sintilimab monotherapy in a relapse pancreatic ductal adenocarcinoma patient with high tumor mutational burden: a case report

Fan Zhang^a, Xiaomin Li^b, Haisheng Liu^a, Rongfeng Liu^a, Zhiguo Zhou^a, Yi Zhang^c, Jingli Chen^c, Ye Tian^c, Chaohu Pan^d, Qingju Meng^{b,*} and Yibing Liu^{a,*}

The reason that immune checkpoint inhibitors have not been widely applied to pancreatic cancer treatment is probably because of low immunogenicity or dense stromal fibrosis. Recently, only pembrolizumab was recommended for DNA mismatch repair deficiency or high microsatellite instability by National Comprehensive Cancer Network guideline. Pancreatic ductal adenocarcinoma (PDAC) accounts for more than 90% of pancreatic cancer, with a poor overall survival rate, the value of immunotherapy for PDAC needs more research. Here, we report a 56-year-old man suffered from PDAC with liver metastasis after radical surgery. The next-generation sequencing result demonstrated that it had remarkably high tumor mutational burden (TMB) of 49.92 Muts/Mb and microsatellite stability. Sintilimab (anti-PD-1) monotherapy was continuously administrated after failure of combined chemotherapy in second line, achieving stable disease within 22 months and few immunotherapy-related adverse events. To our knowledge, this is the first time to report

a good outcome achieving 22 months with progression-free survival after PDAC metastasis with monotherapy of sintilimab. TMB may serve as a potential efficacy-related predictor in PDAC patients with sintilimab and help physicians make optimum clinical strategy. *Anti-Cancer Drugs* 33: 975–978 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

Anti-Cancer Drugs 2022, 33:975–978

Keywords: immunotherapy, pancreatic ductal adenocarcinoma, sintilimab, stable disease, tumor mutational burden

^aDepartment of Medical Oncology, The Fourth Hospital of Hebei Medical University, Shijiazhuang, ^bDepartment of Orthopedics, The First Hospital of Xingtai, Xingtai, ^cHebei Medical University, Shijiazhuang and ^dYuceBio Technology Co., Ltd, Shenzhen, China

Correspondence to Yibing Liu, MD, Department of Medical Oncology, The Fourth Hospital of Hebei Medical University, No.12 JianKang Road, Shijiazhuang, Hebei Province, 050011, China
Tel: +13831173220; e-mail: lyb.he@163.com

Yibing Liu and Qingju Meng contributed equally to the writing of this article.

Received 22 January 2022 Revised form accepted 30 March 2022

Introduction

Pancreatic cancer, with increasing incidence and mortality, has ranked seventh in cancer-related death rate [1]. A study of 28 European countries has projected that it will surpass breast cancer to be the third leading cause of cancer death by 2025 [1,2]. While pancreatic ductal adenocarcinoma (PDAC) accounts for more than 90% of pancreatic tumors, with a 5-year overall survival (OS) rate of 8% [3]. Unfortunately, the majority of patients are diagnosed with locally advanced or metastatic disease due to lack of early detection, as a result that surgery and radiotherapy rarely benefit patients and physicians always have few established treatment strategies to choose [4]. Over the past decades, immunotherapy has led to considerable advances in treatments of various cancers [5,6]. Immune checkpoint inhibitors (ICIs), targeting programmed cell death protein 1 (PD-1), programmed death-ligand 1

(PD-L1) and cytotoxic T-lymphocyte-associated protein 4 have exhibited significant effect in inhibiting cancer cell proliferation, whereas, this success is hardly achieved in PDAC [7], probably due to low tumor mutational burden (TMB), immunosuppressive tumor microenvironment and mismatch repair proficiency [8].

Herein, we report a man suffered from relapse PDAC with remarkably high burden of TMB (49.92 Muts/Mb) and microsatellite stability (MSS) achieved stable disease (SD) within 22 months and had few immunotherapy-related adverse events after third-line sintilimab immunotherapy. We present the following case in accordance with the CARE reporting checklist.

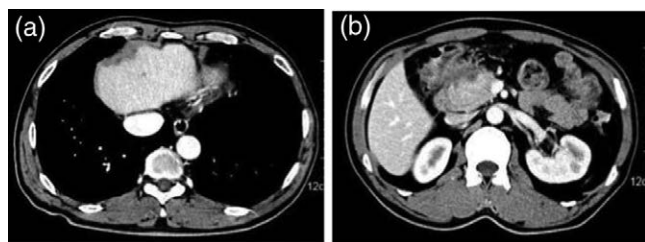
Case presentation

A 56-year-old man was admitted with complaints of intermittent upper abdominal pain and abdominal distension in October 2018. Ultrasonic and computed tomography scans revealed a lesion in right upper abdomen (Fig. 1). Pancreaticoduodenectomy and partial transverse colectomy were performed in November 2018. Postoperative pathology suggested the mass size was 5.5 × 5 × 4.5 cm with duodenum wall involvement, differentiation level II. No vascular tumor emboli, and nerve and lymph node

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.anti-cancerdrugs.com.

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Fig. 1



Computed tomography scans of the liver and pancreas.

involvements. Immunohistochemistry showed AE1/AE3(+), CK20(-), CK7(+), CDX2(±), carcinoembryonic antigen (CEA)(+), Ki67(+60%), Villin(±) and P40(-). The patient was diagnosed with PDAC, stage III (T4N0M0). Four cycles of postoperative adjuvant therapy including gemcitabine (1000 mg/m², day 1 and day 8) plus tegafur (120 mg/day, bid, days 1-14) were administered between December 2018 and February 2019. However, the efficacy was less than satisfactory and liver metastasis was observed based on MRI results (Fig. 2a and b). Then the patient switched to paclitaxel-albumin (260 mg/m²) plus oxaliplatin (100 mg/m²) as second-line chemotherapy in the next 2 months. Unfortunately, after two cycles of treatment, the patient disease progressed with enlarged hepatic metastases (Fig. 2c and d).

To seek for potential therapeutic regimens, peripheral blood sample collected from the patient was detected by next-generation sequencing based on a gene panel that interrogates 1021 cancer-related loci for identification of mutations contributing to effective therapeutic strategies. In summary, two common driver mutations (*KRAS p.G12D* and *PIK3CA p.Q546K*) were found might be associated with targeted therapy in 52 detected somatic mutations. Although erlotinib was accepted in the treatment of pancreatic cancer by National Comprehensive Cancer Network (NCCN), in view of the limited clinical benefit [9] and there is no specific medicine directed against either of the mutations, targeted therapy was not in consideration. Besides, pembrolizumab was approved for high microsatellite instability (MSI-H)/DNA mismatch repair deficiency (dMMR) but MSS was detected in this case. Of great interest, however, remarkably high TMB of 49.92 Muts/Mb was detected, which indicated a large extent of sensitivity to ICIs. Therefore, immunotherapy was applied based on high TMB. The patient, thus, underwent microwave ablation in the liver. After signing informed consent, sintilimab (200 mg) was administered at 21-day intervals from May 2019. Soon, liver lesions were effectively controlled and SD was obtained within 2-month monotherapy (Fig. 2e and f). The patient continued sintilimab treatment and efficacy maintained SD by evaluation in March 2021 and disease

progression has not been reached (Fig. 2g and h). The treatment timeline and tumor evaluation is presented in Fig. 3. Treatment-related adverse events were diarrhea and thyroid function test abnormal, which were both grade I (Supplementary Fig. 1, Supplemental Digital Content 1, <http://links.lww.com/ACD/A439>). The serum tumor marker level reached the top of CEA at 6.49 ng/ml and CA19-9 at 19.3 U/ml before immunotherapy and decreased after sintilimab administration (Supplementary Fig. 2, Supplemental Digital Content 1, <http://links.lww.com/ACD/A439>). Chemistry and complete blood count data showed that the related indexes gradually tended to be normal after sintilimab treatment (Supplementary Table1, Supplemental Digital Content 2, <http://links.lww.com/ACD/A440>).

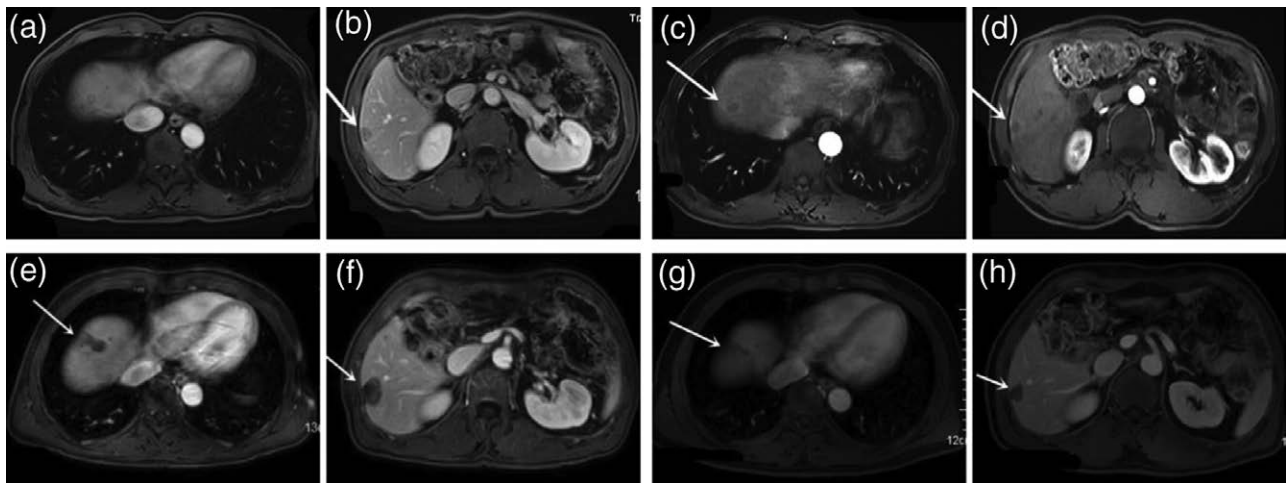
Discussion

PDAC is one of the most aggressive and lethal cancers with a median OS of only 6.9 months for liver metastases patients [10]. Increased median OS has been obtained of 8.5 months when treated with nabpaclitaxel-gemcitabine [11]. In recent years, immunotherapy has become a new hotspot in antitumor therapy and has achieved good efficacy in many solid tumors. However, there is little progress in the treatment of pancreatic cancer, which is attributed to its immunosuppressive microenvironment and poor T cell infiltration [8]. Among the checkpoint blockades, no established strategy is indicated beyond pembrolizumab, which has been recommended for patients with MSI-H/dMMR advanced pancreatic cancer by NCCN. However, MSI-H/dMMR presents a rare prevalence of about 1-2% in PDAC cases [12]. Furthermore, durvalumab and tremelimumab were involved in a phase 2 randomized clinical trial, which showed poor objective response rate (3.1%) of durvalumab combined with tremelimumab therapy and no objective response rate (0%) of durvalumab monotherapy to metastatic PDAC, resulting in poor prognosis and rapidly progressing disease [13]. Thus, the successful implementation of immunotherapy in pancreatic cancer has a long way to go.

Sintilimab, an engineered PD-1 inhibitor blocking the interaction between PD-1 and its ligands, has shown better PD-1 binding capacity than nivolumab and pembrolizumab *in vitro* and durable PD-1 receptor occupancy rate in patients [14]. With a broad spectrum of antineoplastic effect including nonsmall cell lung cancer (NSCLC) [15], hepatocellular carcinoma [16], gastric/gastroesophageal junction adenocarcinoma [17] and lymphoma [18]. Moreover, sintilimab makes it affordable for a long-term use by its economic advantage.

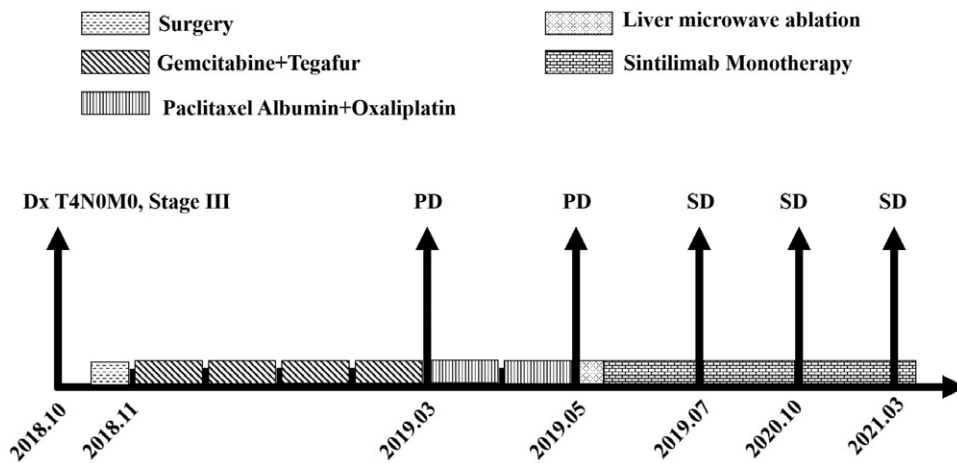
PDAC is thought for low immunogenic or stromal fibrotic tumors, but the case here obtained a considerable benefit from a PD-1 inhibitor with PFS exceeding 21 months after unsuccessful chemotherapy. Conversely, the median OS of stage IV PDAC patients with liver metastasis is

Fig. 2



MRI of liver in different treatment phases. Liver metastasis was found after four cycles treatment of gemcitabine and tegafur.

Fig. 3



The timeline from diagnosis of PDAC to different stages of therapeutic regime and evaluation. Dx, diagnosis; PDAC, pancreatic ductal adenocarcinoma.

only 3 months and is even worse after chemotherapy failure. We have searched literatures including both ‘sintilimab’ and ‘pancreatic cancer’, there is no related study involving sintilimab as immunotherapeutic in pancreatic cancer reported, even in combination therapy. To our knowledge, we for the first time reported sintilimab monotherapy showed surprising outcome in liver metastasis PDAC patient with high TMB.

TMB as an emerging biomarker for predictive clinical outcome from immune checkpoint blockades has been confirmed in melanoma, lung cancer and urothelial carcinoma [8]. High TMB, indicating less genomic stability, is usually considered to promote neoantigens production

and further enhance immunogenicity. Samstein *et al.* conducted an analysis to explore the association between somatic TMB and response to ICI in a variety of cancer types. The results suggested higher TMB was correlated with better objective response rate or longer survival in patients receiving ICI [19]. In addition, Food and Drug Administration has approved pembrolizumab for the treatment of solid tumors with high-tissue TMB, which was defined as at least 10 Mut/Mb in June 2020. TMB has been commonly detected in DNA from tumor tissue, but the resected tissue could have not demonstrated mutation status at the moment of liver metastasis in our presenting case. Besides, tissue is not always easy to obtain clinically. Alternatively, blood TMB from plasma cell-free

DNA has been supported as a potential predictor of clinical benefit in NSCLC patients treated with immunotherapy [20]. Besides, Shi *et al.* [21] verified the reliability of ctDNA for predicting or monitoring the response to sintilimab immunotherapy in 192 plasma samples from 75 patients with relapsed or refractory classical Hodgkin lymphoma.

In conclusion, this is the first case that sintilimab monotherapy has reached effectively disease control and quickly response in a PDAC patient with high TMB. TMB can be used as a potential predictor of sintilimab for PDAC patients to help physicians formulate the best clinical strategy. Nevertheless, more studies are needed for better understanding of the effectiveness and safety of sintilimab immunotherapy in PDAC patients with high TMB.

Acknowledgements

This study has been approved by the Fourth Hospital of Hebei Medical University Ethics Committee and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The informed consent was obtained from the patient.

Conflicts of interest

There are no conflicts of interest.

References

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; **71**:209–249.
- Ferlay J, Partensky C, Bray F. More deaths from pancreatic cancer than breast cancer in the EU by 2017. *Acta Oncol* 2016; **55**:1158–1160.
- Chiaravalli M, Reni M, O'Reilly EM. Pancreatic ductal adenocarcinoma: state-of-the-art 2017 and new therapeutic strategies. *Cancer Treat Rev* 2017; **60**:32–43.
- Adamska A, Domenichini A, Falasca M. Pancreatic ductal adenocarcinoma: current and evolving therapies. *Int J Mol Sci* 2017; **18**:E1338.
- Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, *et al.* Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015; **373**:1627–1639.
- Sharma P, Callahan MK, Bono P, Kim J, Spiliopoulou P, Calvo E, *et al.* Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial. *Lancet Oncol* 2016; **17**:1590–1598.
- Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, *et al.* Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother* 2010; **33**:828–833.
- Sarantis P, Koustas E, Papadimitropoulou A, Papavassiliou AG, Karamouzis MV. Pancreatic ductal adenocarcinoma: treatment hurdles, tumor microenvironment and immunotherapy. *World J Gastrointest Oncol* 2020; **12**:173–181.
- Chiorean EG, Covelev AL. Pancreatic cancer: optimizing treatment options, new, and emerging targeted therapies. *Drug Des Devel Ther* 2015; **9**:3529–3545.
- Liu KH, Hung CY, Hsueh SW, Chang PH, Chen YY, Lu CH, *et al.* Lung metastases in patients with stage IV pancreatic cancer: prevalence, risk factors, and survival impact. *J Clin Med* 2019; **8**:E1402.
- Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, *et al.* Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* 2013; **369**:1691–1703.
- Luchini C, Brosens LAA, Wood LD, Chatterjee D, Shin JI, Sciammarella C, *et al.* Comprehensive characterisation of pancreatic ductal adenocarcinoma with microsatellite instability: histology, molecular pathology and clinical implications. *Gut* 2021; **70**:148–156.
- O'Reilly EM, Oh DY, Dhani N, Renouf DJ, Lee MA, Sun W, *et al.* Durvalumab with or without tremelimumab for patients with metastatic pancreatic ductal adenocarcinoma: a phase 2 randomized clinical trial. *JAMA Oncol* 2019; **5**(10):1431–1438.
- Wang J, Fei K, Jing H, Wu Z, Wu W, Zhou S, *et al.* Durable blockade of PD-1 signaling links preclinical efficacy of sintilimab to its clinical benefit. *MAbs* 2019; **11**:1443–1451.
- Gao S, Li N, Gao S, Xue Q, Ying J, Wang S, *et al.* Neoadjuvant PD-1 inhibitor (Sintilimab) in NSCLC. *J Thorac Oncol* 2020; **15**:816–826.
- Chen J, Hu X, Li Q, Dai W, Cheng X, Huang W, *et al.* Effectiveness and safety of toripalimab, camrelizumab, and sintilimab in a real-world cohort of hepatitis B virus associated hepatocellular carcinoma patients. *Ann Transl Med* 2020; **8**:1187.
- Jiang H, Zheng Y, Qian J, Mao C, Xu X, Li N, *et al.* Safety and efficacy of sintilimab combined with oxaliplatin/capecitabine as first-line treatment in patients with locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma in a phase Ib clinical trial. *BMC Cancer* 2020; **20**:760.
- Shi Y, Su H, Song Y, Jiang W, Sun X, Qian W, *et al.* Safety and activity of sintilimab in patients with relapsed or refractory classical Hodgkin lymphoma (ORIENT-1): a multicentre, single-arm, phase 2 trial. *Lancet Haematol* 2019; **6**:e12–e19.
- Samstein RM, Lee CH, Shoushtari AN, Hellmann MD, Shen R, Janjigian YY, *et al.* Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nat Genet* 2019; **51**:202–206.
- Wang Z, Duan J, Cai S, Han M, Dong H, Zhao J, *et al.* Assessment of blood tumor mutational burden as a potential biomarker for immunotherapy in patients with non-small cell lung cancer with use of a next-generation sequencing cancer gene panel. *JAMA Oncol* 2019; **5**:696–702.
- Shi Y, Su H, Song Y, Jiang W, Sun X, Qian W, *et al.* Circulating tumor DNA predicts response in Chinese patients with relapsed or refractory classical hodgkin lymphoma treated with sintilimab. *EBioMedicine* 2020; **54**:102731.