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Research Article

Keywords: Pancreatic ductal adenocarcinoma, immunotherapy, tumor mutational burden, stable disease, progression-free survival, sintilimab.

Posted Date: August 26th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-789622/v1>

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Unexpected Favorable Outcome to Sintinib Monotherapy in a Relapse PDAC Patient with High TMB

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Abstract

Background

Immune checkpoint inhibitors have not been widely used for pancreatic cancer
treatment probably because of low immunogenic or stromal fibrotic tumor, among
which only pembrolizumab was recommended for DNA mismatch repair deficiency
(dMMR) by NCCN.

Case presentation

Here we report a 56-year-old man suffered from pancreatic ductal cancer (PDAC) with liver metastasis after radical surgery. NGS revealed remarkably high burden of TMB (49.92Muts/Mb) and microsatellite stability (MSS). Sintilimab monotherapy was continuously administrated after failure of combined chemotherapy, leading to stable disease within 22 months and few immunotherapy related AEs happened.

Conclusions

To our best knowledge, this is the first to report a good outcome achieving 22 months progression-free survival after PDAC metastasis with monotherapy of an immune checkpoint inhibitor. TMB may serve as a potential immunotherapy-related predictor in PDAC patients and help physicians make optimum clinical strategy.

Keywords: Pancreatic ductal adenocarcinoma, immunotherapy, tumor mutational burden, stable disease, progression-free survival, sintilimab.

Background

Pancreatic cancer, with both increasing incidence and mortality, has reached the seventh cancer-related death [1]. A study of 28 European counties 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, 4] . 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

50 and physicians always have few established treatment strategy to choose [5, 6].
51 Nevertheless, few targeted agent has been developed for pancreatic cancer except
52 erlotinib recommended by the guidance of National Comprehensive Cancer Network
53 (NCCN). Despite commonly found mutations of *KRAS* and inactivating mutations of
54 *CDK2NA*, *TP53*, *DPC4/SMAD4* [7], no uniform success was achieved by single
55 molecular target therapy in PDAC, probably due to the tumor heterogeneity[8]. As
56 highly reactive and dense stromal within the PDAC associated with aggressiveness and
57 drug resistance, PDAC prognosis is always poor and leads to tumor progression[9] .

58 Over the past decade, immunotherapy has led to considerable advances in
59 treatments of variety cancers [10, 11]. Checkpoint inhibitors, targeting programmed
60 cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-
61 lymphocyte-associated protein 4 (CTLA-4) have exhibited significant effect in
62 inhibiting cancer cell proliferation, whereas, this success has been hardly achieved in
63 PDAC [12], probably due to low tumor mutational burden (TMB), immunosuppressive
64 tumor microenvironment and mismatch repair proficiency[13, 14].

65 Herein, we report a 56-year-old man suffered from pancreatic ductal cancer
66 (PDAC) with remarkably high burden of TMB (49.92Muts/Mb) and microsatellite
67 stability (MSS). Sintilimab monotherapy was administrated after radical surgery and
68 failure of combined chemotherapy, and has maintained continuously stable disease
69 within the next 22 months treatment and few immunotherapy related AEs happened.

70 **Case presentation**

A 56-year-old man was admitted with complaints of intermittent upper abdominal pain and abdominal distension in Oct 2018. Ultrasonic and computed tomography (CT) scans revealed a lesion in right upper abdomen (Fig.1). Pancreaticoduodenectomy and partial transverse colectomy were performed in Nov 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, nerve and lymph node involvement. Immunohistochemistry showed AE1/AE3(+), CK20(-), CK7(+), CDX2(+/-), 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, day1 and day8) plus tegafur (120 mg/day, bid, day1-14) 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-B). Then the patient switched to paclitaxel-albumin (260 mg/m²) plus oxaliplatin (100 mg/m²) as second line chemotherapy in the next two months. Unfortunately, after two cycles of treatment, the patient disease progressed with enlarged hepatic metastases (Fig.2 C-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 which interrogates 1021 cancer-related loci for identification of mutations contributing to effective therapeutic strategies. In summary, two common driver mutations (*KRAS* *p.G12D*, *PIK3CA* *p.Q546K*) were found might be associated with targeted therapy in 52 detected somatic mutations. Although erlotinib was accepted in treatment of pancreatic cancer by NCCN, in view of the limited clinical benefit [8] and there is no

specific medicine directed against either of the mutations, targeted therapy was not in consideration. Besides, pembrolizumab was approved for MSI-H/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 immune checkpoint inhibitors (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 administrated at 21-day intervals from May 2019. Soon, liver lesions were effectively controlled and stable disease (SD) was obtained within two-month monotherapy (Fig.2 E-F). The patient continued sintilimab treatment and efficacy maintained SD by evaluation in March 2021 and disease progression has not been reached (Fig.2 G-H). The treatment timeline and tumor evaluation is presented in Figure 3. Treatment-related adverse events were diarrhea and thyroid function test abnormal which were both grade I (Supplementary Fig.1). 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)

Discussion

PDAC is one of the most aggressive and lethal cancers with a median overall survival of only 6.9 months for isolated liver metastases patients [15]. Increased median overall survival has been obtained of 8.5 months when treated with nabpaclitaxel–gemcitabine [16]. In recent years, immunotherapy has become a new hotspot in anti-tumor therapy, and has achieved good efficacy in many solid tumors. However, there

is little progress in the treatment of pancreatic cancer, which is responsible for its immunosuppressive microenvironment and poor T cell infiltration [13]. 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 [17]. 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 [18]. 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 [19]. With a broad spectrum of antineoplastic effect including non-small cell lung cancer[20], hepatocellular carcinoma[21], gastric/gastroesophageal junction adenocarcinoma[22] and lymphoma[23] , sintilimab has been approved for relapsed classical Hodgkin's lymphoma and sintilimab combined with chemotherapeutics has been approved for nonsquamous non-small cell lung cancer without epidermal growth factor receptor or anaplastic lymphoma kinase mutation based on ORIENT-11 study [24]. Moreover, sintilimab make 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 overall survival of in stage IV PDAC patients with liver metastasis is only 3 months and is even worse after chemotherapy failure. We've searched literatures including both 'sintilimab' and 'pancreatic cancer', there's no related study involving sintilimab as immunotherapeutic in pancreatic cancer reported, even in combination therapy. To our best knowledge, we for the first time report sintilimab monotherapy showed surprising outcome in liver metastasis PDAC after failure of second-line combination chemotherapy.

TMB as an emerging biomarker for predictive clinical outcome from immune checkpoint blockades has been confirmed in melanoma, lung cancer, and urothelial carcinoma [14, 25, 26]. 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 type. The results suggested higher TMB was correlated with better objective response rate or longer survival in patients receiving ICI [25]. In addition, FDA has approved pembrolizumab for the treatment of solid tumors with high tissue TMB (tTMB) which was defined as ≥ 10 Mut/Mb in June 2020. The approval was based on efficacy evidence from 10 refractory solid tumor cohorts [27]. 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 easily 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 PD-1 and anti-PD-L1 agents [28, 29]. Besides, Shi et al. 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 [30].

Conclusions

This is the first report that sintilimab monotherapy have reached effectively disease control and quickly response in a PDAC patient. TMB may serve as a potential immunotherapy-related predictor in PDAC patients and help physicians make optimum clinical strategy. Nevertheless, more studies are needed for better understanding of the effectiveness and safety of sintilimab immunotherapy in PDAC patients with high TMB.

List of abbreviations

Pancreatic ductal adenocarcinoma (PDAC), programmed death 1 (PD-1), programmed death-ligand 1 (PD-L1), microsatellite instability stable (MSS), tumor mutational burden (TMB), stable disease (SD), progressive disease (PD), progression-free survival (PFS), immune checkpoint inhibitors (ICI).

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

Availability of data and materials

All data generated or analyzed during this current study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

Funding

None

Authors' contributions

HSL and XML contributed the same to this manuscript. RFL, ZGZ, YBL and CHP acquired the data and created a draft of the manuscript; YZ, ZT, QJM and JLC, XML collected the data; YBL and QJM revised and approved the final version of the manuscript. All authors read and approved the final version of this submitted manuscript.

Acknowledgements

Not applicable.

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Figures

Figure 1

Computed tomography scans of the liver and pancreas.

Figure 2

Magnetic resonance imaging (MRI) of liver in different treatment phases. Liver metastasis was found after four cycles treatment of gemcitabine and tegafur, (A) and (B). Liver lesions were enlarged after combined therapy of Paclitaxel Albumin and oxaliplatin, (C) and (D). After Liver microwave ablation and sintilimab monotherapy for two months, lesions were stable, (E) and (F). Continued sintilimab monotherapy for another twenty months, lesions were controlled well, (G) and (H).

Figure 3

The timeline from diagnosis of PDAC to different stages of therapeutic regime and evaluation. Dx means diagnosis.

Supplementary Files

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