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ORIGINAL ARTICLE

Immune checkpoint inhibitors combined with chemotherapy for the treatment of advanced pancreatic cancer patients

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Abstract

Immune checkpoint inhibitors (ICIs) represent a major breakthrough for cancer treatment. However, evidence regarding the use of ICIs in pancreatic cancer (PC) remained scarce. To assess the efficacy and safety of ICIs plus chemotherapy, patients with advanced PC were retrospectively recruited and were treated with either chemotherapy alone or chemotherapy plus ICIs. Patients previously treated with any agents targeting T-cell co-stimulation or checkpoint pathways were excluded. The primary outcome was overall survival (OS). The secondary outcomes were progression-free survival (PFS), overall response rate (ORR) and safety. In total, 58 patients were included (combination, $n=22$; chemotherapy, $n=36$). The combination group showed a significantly longer OS than the chemotherapy group [median, 18.1 vs 6.1 months, hazard ratio (HR) 0.46 (0.23–0.90), $P=0.021$]. The median PFSs were 3.2 months in the combination group and 2.0 months in the chemotherapy group [HR 0.57 (0.32–0.99), $P=0.041$]. The combination group and the chemotherapy group had similar ORRs (18.2% vs 19.4%, $P=0.906$). All patients who achieved a partial response received a doublet chemotherapy regimen regardless of co-treatment with ICIs. Grade 3 or higher adverse events occurred in 31.8% of the patients in the combination group and in 16.9% of those receiving chemotherapy. Although the incidence of serious treatment-related adverse events was higher in the combination group than in the chemotherapy group, the difference was not significant ($P=0.183$). Our findings suggest that the combination of ICIs with chemotherapy is both effective and tolerable for advanced PC. ICIs combined with a doublet chemotherapy regimen might be a preferable choice.

Keywords Pancreatic cancer · Immune checkpoint inhibitors · Combination therapy · Efficacy · Safety

Abbreviations

ASCO	American Society of Clinical Oncology
ASCO-GI	American Society of Clinical Oncology-gastrointestinal cancer
CR	Complete response
DCR	Disease control rate
ECOG	Eastern Cooperative Oncology Group
FOLFIRINOX	Fluorouracil/leucovorin plus irinotecan plus oxaliplatin
GEST	Gemcitabine and S-1 Trial
HR	Hazard ratio
ICI	Immune checkpoint inhibitor
dMMR	Mismatch repair deficient
mOS	Median overall survival
mPFS	Median progression-free survival
MSI-H	Microsatellite instability-high
ORR	Overall response rate
PC	Pancreatic cancer
PR	Partial response
PS	Performance status
SD	Stable disease
TRAE	Treatment-related adverse event

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Junxun Ma and Danyang Sun are co-first authors.

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Introduction

Pancreatic cancer (PC), a highly lethal disease as reflected by its high incidence and mortality, is usually asymptomatic and most patients are diagnosed with advanced disease [2–4]. Surgery provides the only potential possibility for a cure, however, only less than 20% of patients are eligible for resection, and most patients still eventually recur [3]. For advanced PC, gemcitabine or two combination therapies [gemcitabine with nab-paclitaxel and fluorouracil/leucovorin plus irinotecan plus oxaliplatin (FOLFIRINOX)] have been widely acknowledged as the standard systemic therapies since 2010 [5–7]. However, published data indicated that the clinical benefit of chemotherapy was still far from ideal. For example, among patients with advanced-stage PC, the 5-year survival rate after standard chemotherapy is only 2% [2]. Given the lack of effective treatment, considerable efforts have been devoted to improving the outcomes of patients with advanced PC.

Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) or PD-1 ligand (PD-L1) have emerged as promising treatment strategies in cancer care that lead to durable antitumor activities and improved survival in various malignancies [8–10]. However, there is limited evidence on the efficacy of ICIs in PC. The PD-1 inhibitor pembrolizumab appeared to be efficacious in a subset of PC patients who were microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) [11]. However, the prevalence of dMMR/MSI-H is low in PC, as shown by genetic profiling of 385 PC cases where a hypermutated profile (all related to dMMR) was found in only less than 2% (4/385) of the cases [12]. In addition, two phase I trials and one phase II trial demonstrated that anti-PD-1/PD-L1 monotherapy failed to elicit any response in unselected advanced PC patients [13–15]. Hence, overall, except for MSI-H tumors, PCs are considered resistant to single-agent immunotherapy. Based on published research, there are three major hurdles to overcome before immunotherapy could be widely applied in PC treatment: a low level of mutational load [16], a largely immunosuppressive microenvironment [17], and few infiltrating T cells [18]. Thus, the incorporation of additional therapies that can convert the "cold" microenvironment to a "hot" one becomes a key strategy to enhance the clinical activity of immunotherapy.

Chemotherapy may promote the release of tumor neoantigens by inducing tumor cell death, which in turn triggers an anticancer immune response [19]. Immunotherapy administered alongside chemotherapy is predicted to synergistically enhance the antitumor effects of either therapy alone [20]. For advanced PC, ICIs combined with chemotherapy have been investigated. In a phase II study, pembrolizumab plus doublet chemotherapy in metastatic PC achieved an overall response rate (ORR) of 20.0% (3/15) and a disease control rate (DCR) of 86.7% (13/15) [21]. Another study presented at the 2018 American Society of Clinical Oncology-gastrointestinal cancer (ASCO-GI) meeting showed that nivolumab combined with three chemotherapeutic drugs produced a DCR of 100% and an ORR of 80% [22]. However, these two studies were both single armed. A prospective cohort study of two ICIs (PD-1 inhibitor and CTLA-4 inhibitor) plus chemotherapy compared with chemotherapy alone showed that combination therapy was both effective and tolerable [23]. Although this strategy significantly improved the therapeutic effect, it was unclear which drug played a major role since two different ICIs were utilized. Moreover, such a complex treatment regimen might also increase cost and toxicity.

Herein, we evaluated the efficacy and safety of ICIs plus chemotherapy compared with chemotherapy alone for advanced PC. This study may improve our understanding of the effects of immunotherapy combined with chemotherapy on PC.

Patients and methods

Participants and study design

Patients with unresectable advanced PC having been treated with at least one cycle of anti-PD-1/PD-L1 combination therapy or chemotherapy between June 2015 and May 2018 at the People's Liberation Army General Hospital (Beijing) were retrospectively included. To ensure data quality, the protocol, case report form (CRF), and standard operating procedure (SOP) of data collection were prospectively designed before the launch of this study.

Patients were identified via electronic medical records based on the following eligibility criteria: (1) biopsy confirmed metastatic PC and (2) received at least one cycle of ICIs plus chemotherapy or chemotherapy. Patients who had been previously exposed to any agent targeting T-cell costimulation or immune checkpoints were excluded from this study.

Data collection and study objectives

Two investigators independently extracted and verified information on the clinico-pathological characteristics and treatment histories of the patients. All imaging data were independently assessed by two physicians. Any inconsistent evaluation results were further determined by the director

of the imaging center. The data were last edited on Oct 30, 2018.

Overall survival (OS) was the primary outcome and was defined as the time from the treatment initiation to death for any reason. The secondary outcomes included progression-free survival (PFS), ORR, DCR and safety (treatment-related adverse events). PFS was defined as the time from the treatment initiation to disease progression or death by any cause. ORR [the percentage of patients with a confirmed complete/partial response (CR/PR)] and DCR [the proportion of patients with CR, PR, or stable disease (SD)] were assessed according to the RECIST criteria [24]. Data on adverse events were collected according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [25]. Patients who were alive and did not experience any of these events were censored on the date of the last follow-up. The study was reported according to the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) [26].

Statistical analysis

Patients who did not complete the first cycle of treatment were replaced in the final study outputs. The baseline characteristics and response data between the two groups were compared using the Chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous or ordinal variables. OS and PFS were analyzed using the Kaplan–Meier method with a *P* value determined by the log-rank test. Hazard ratios (HR) were estimated using Cox proportional hazards regression. Two-sided *P* values were evaluated and $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS statistical software (version 20.0, IBM Corporation, USA) and GraphPad Prism (version 6, GraphPad Software Inc., USA).

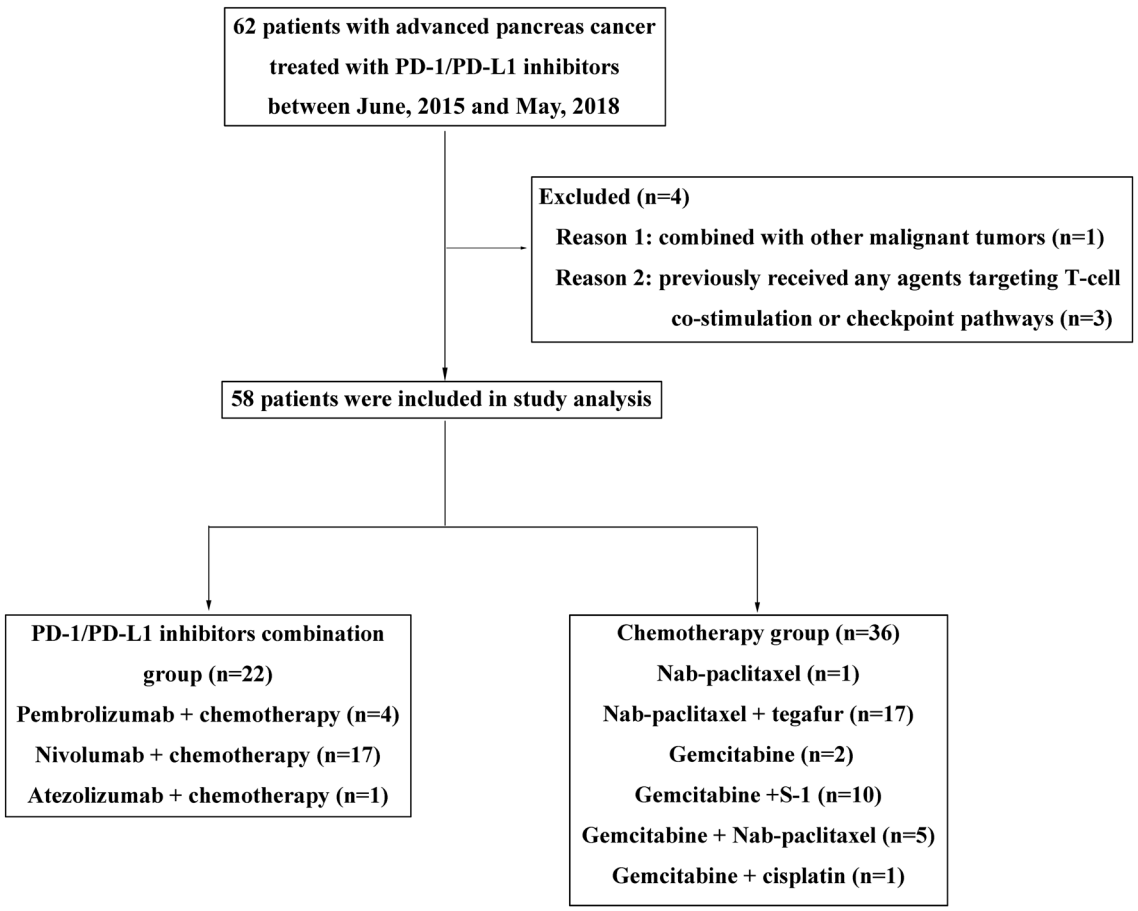

Fig. 1 Flow diagram of the study

Results

Patient and tumor characteristics

A total of 58 patients with metastatic PC were enrolled in this study, 36 patients treated with chemotherapy (chemotherapy group) and 22 patients treated with a combination of ICIs and chemotherapy (combination group) (Fig. 1). In the chemotherapy group, the most common regimen was nab-paclitaxel plus tegafur (47.2%, 17/36), and only three patients received a single chemotherapeutic drug. In the combination group, 17 patients were treated with nivolumab plus chemotherapy, 4 with pembrolizumab plus chemotherapy, and 1 with atezolizumab plus chemotherapy. The treatment strategy for each individual is shown in Supplementary Table S1. The patients' baseline characteristics are shown in Table 1, and most demographics and disease characteristics were in general well balanced between the two groups. Both groups had a higher percentage of males than females. The majority of patients never smoked or consumed alcohol, and most of the patients had an ECOG performance status (PS) of 0–2. The liver and lymph nodes were the most common sites of metastases. Approximately one-third of the patients in both groups had undergone surgery. In addition, treatment-naive patients were more common in the chemotherapy group than in the combination group (97.7% vs 72.3%, $P=0.016$).

Table 1 Baseline characteristics

Characteristics	Combination group ($n=22$)	Chemotherapy group ($n=36$)	P value
Median age, years (range)	56.0 (34–73)	54.0 (30–77)	0.573
Sex, *n* (%)			0.955
Male	13 (59.1%)	21 (58.3%)	
Female	9 (40.9%)	15 (41.7%)	
Alcohol history, *n* (%)			0.967
Former or current	6 (27.3%)	10 (27.8%)	
Never or unknown	16 (72.7%)	26 (72.2%)	
Pancreatic tumor location, *n* (%)			0.484
Head	12 (54.5%)	23 (63.0%)	
Body or tail	10 (45.5%)	13 (36.1%)	
Smoking history, *n* (%)			0.673
Former or current	5 (22.7%)	10 (27.8%)	
Never or unknown	17 (77.3%)	26 (72.2%)	
ECOG performance status, *n* (%)			0.261
0–2	21 (95.5%)	31 (86.1%)	
> 2	1 (4.5%)	5 (13.9%)	
Previous surgery, *n* (%)			0.092
Yes	8 (36.4%)	6 (16.7%)	
No	14 (63.6%)	30 (83.3%)	
Number of prior lines of treatment for metastatic disease, *n* (%)			0.016
0	17 (72.3%)	35 (97.2%)	
≥ 1	5 (22.7%)	1 (2.8%)	
Site of metastases, *n* (%)			
Liver	20 (90.9%)	29 (80.6%)	0.295
Lymph node	20 (90.9%)	31 (86.1%)	0.590
Lung	5 (22.7%)	4 (11.1%)	0.240
Peritoneal	4 (18.2%)	6 (16.7%)	0.883
Other	5 (22.7%)	8 (22.2%)	0.965
Number of metastases			0.484
0–2	12 (54.5%)	23 (63.9%)	
≥ 3	10 (45.5%)	13 (36.1%)	

ECOG Eastern Cooperative Oncology Group

Efficacy

The median follow-up for all patients after the commencement of study treatment was 6.9 months (range 2.0–29.1 months). In total, 56 (96.6%) patients experienced disease progression and 48 (82.6%) patients died. The median OS (mOS) was 18.1 months (95%

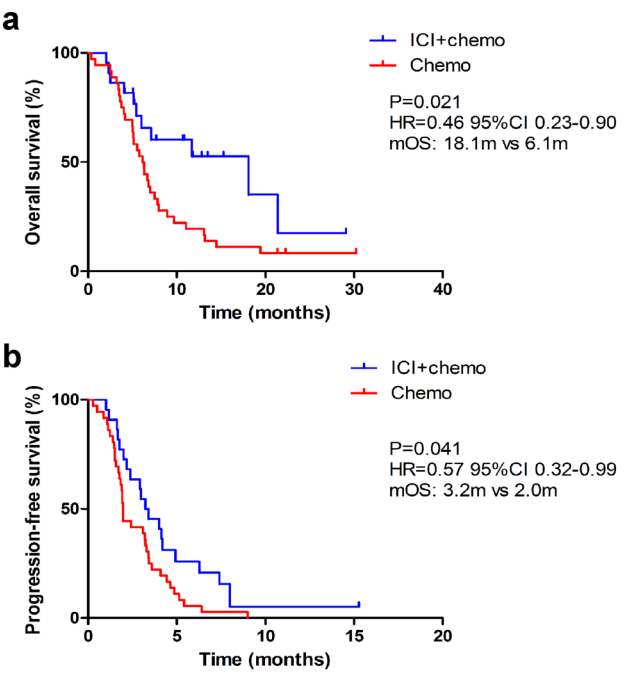

Fig. 2 Kaplan–Meier estimates of overall survival (**a**) and progression-free survival (**b**) comparing chemotherapy alone and chemotherapy combined with immune checkpoint inhibitors (ICIs). *mOS* median overall survival, *HR* hazard ratio, ICI + chemo the group of patients receiving immune checkpoint inhibitors and chemotherapy, Chemo the group of patients receiving chemotherapy

Table 2 Tumor response to treatment for the overall population

	Combination group ($n=22$)	Chemotherapy group ($n=36$)	P value
Objective response, n (%; 95% CI)	4 (18.2%; 6.5–36.9)	7 (19.4%; 9.5–33.5)	0.906
Disease control rate, n (%; 95% CI)	13 (59.1%; 39.5–76.7)	21 (58.3%; 67.0–88.9)	0.955
Best overall response, n (%)			
Complete response	0	0	
Partial response	4 (18.2)	7 (19.4%)	
Stable disease	9 (40.9%)	14 (38.9%)	
Progressive disease	9 (40.9%)	15 (41.7%)	

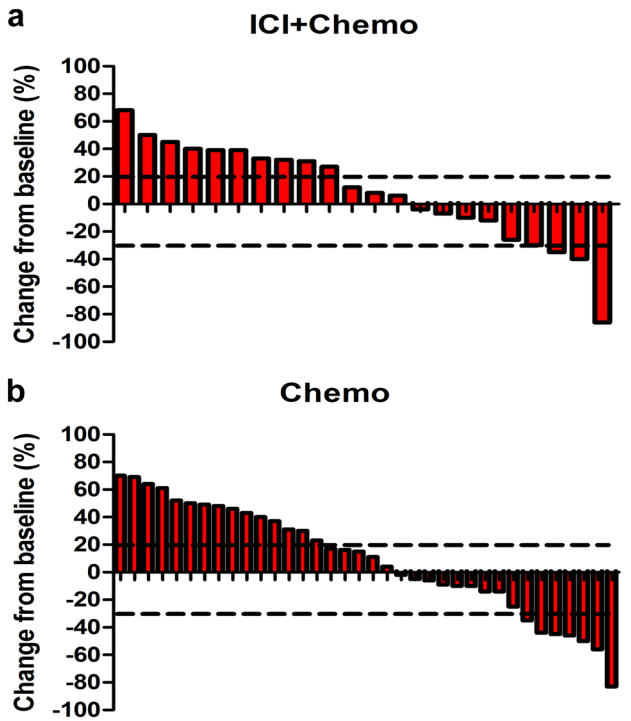

Fig. 3 Waterfall plots of the best percentage change. **a** The best percentage change in tumor size from baseline for individual patients in the combination immunotherapy group. **b** The best percentage change in tumor size from baseline for individual patients in the chemotherapy group. ICI + chemo the group of patients receiving immune checkpoint inhibitors and chemotherapy, Chemo the group of patients receiving chemotherapy

Table 3 Treatment-related adverse events

	Combination group ($n=22$)		Chemotherapy group ($n=36$)	
	Grade 1–4	Grade 3–4	Grade 1–4	Grade 3–4
Any term[a]	19 (86.4%)	7 (31.8%)	30 (83.3%)	6 (16.7%)
Nausea	6 (27.3%)	1 (4.5%)	15 (41.7%)	1 (2.8%)
Diarrhea	1 (4.5%)	0	0	0
Fever	1 (4.5%)	0	0	0
Fatigue	1 (4.5%)	0	0	0
Anemia	1 (4.5%)	0	4 (11.1%)	0
Creatinine	0	0	2 (5.6%)	0
Skin rash	0	0	1 (2.7%)	0
Neurotoxicity	0	0	8 (22.2%)	1 (2.8%)
Pulmonitis	1 (4.5%)	0	0	0
AST elevation	2 (4.5%)	0	0	0
ALT elevation	0	0	0	0
Thrombocytopenia	5 (22.7%)	2 (9.1%)	3 (8.3%)	2 (5.6%)
Leukopenia	1 (9.1%)	0	0	0
Neutropenia	9 (40.9%)	3 (13.6%)	22 (61.1%)	3 (8.3%)

AST aspartate aminotransferase, *ALT* alanine aminotransferase

[a]Listed are all adverse events that occurred during the whole treatment process regardless of attribution to any treatment regimens

CI 4.0–32.2) in the combination group and 6.1 months (95% CI 5.0–7.3) in the chemotherapy group (HR 0.46, 95% CI 0.23–0.90, $P=0.021$, Fig. 2a). The median PFS (mPFS) was 3.2 months (95% CI 2.0–4.5) in the combination group compared with 2.0 months (95% CI 1.9–2.0) in the chemotherapy group with an HR of 0.57 (95% CI 0.32–0.99) ($P=0.041$, Fig. 2b). OS and PFS analyses of subgroups stratified according to baseline demographics and disease characteristics showed that most subgroups obtained greater clinical benefits from ICIs plus chemotherapy than from chemotherapy alone (Supplementary Figure S1). In particular, patients with no prior surgical treatment or fewer metastases presented with a significantly longer mOS with combination treatment, and patients with liver metastases also had a significantly longer mPFS when treated with ICIs plus chemotherapy rather than chemotherapy alone.

As of data cut-off, the ORRs were similar between the combination group and the chemotherapy group (18.2% vs 19.4%), and the difference was not statistically significant ($P=0.906$, Table 2 and Fig. 3). In addition, 59.1% (13/22) of the patients who received ICIs plus chemotherapy achieved disease control while the DCR for the chemotherapy group was 58.3% (21/36) ($P=0.955$). The median change from baseline was 10% (range − 86 to 68%) for the combination immunotherapy group and 13% (range − 83 to 70%) for the chemotherapy group.

Safety

All the treatment-related adverse events (TRAEs) are shown in Table 3. Most TRAEs were grades 1–2 with a predominance of neutropenia (6 out of 13 patients on ICIs plus chemotherapy and 19 out of 36 patients on chemotherapy). The incidence of grade 3–4 TRAEs was higher in the combination group (31.8%) than in the chemotherapy group (16.7%), but the difference was not statistically significant ($P = 0.183$). In the combination group, the most common serious TRAEs were neutropenia (3/22, 13.6%), thrombocytopenia (2/22, 9.1%), and nausea (1/22, 4.5%) and the chemotherapy group followed a similar pattern with 8.3% (3/36) neutropenia, 5.6% (2/36) thrombocytopenia, and 2.8% (1/36) nausea. No autoimmune events or drug-related deaths occurred in either group.

Discussion

This retrospective study evaluated the efficacy and safety of chemotherapy alone or in combination with ICIs in PC patients who were treatment-naive or had progressed on prior chemotherapy. Our study demonstrated in a cohort of 58 such patients that adding ICIs to conventional chemotherapy resulted in an approximately 50% reduction in the risk of death. Although ICIs combined with chemotherapy was not associated with a higher ORR or DCR, the mOS and mPFS were significantly prolonged. The trend of greater survival benefits associated with the ICI combination was also observed in all subgroups. Significantly improved survival was observed in the subgroups with no previous surgical treatment or fewer metastatic sites. In addition, ICIs plus chemotherapy was tolerable without unexpected toxicity. Collectively, this retrospective study showed that introducing immunotherapy into conventional chemotherapy may have a favorable effect on patients' outcomes.

In both groups, the patients who achieved PR were all treated with a doublet chemotherapy regimen rather than single-agent chemotherapy regimen, whether combined with ICIs or not. In previous research, gemcitabine-based chemotherapy or targeted therapy has generally not demonstrated a significant survival benefit over gemcitabine monotherapy [27]. It was not until a decade ago that accumulating evidence started to show that combination chemotherapy regimens, e.g., nab-paclitaxel plus gemcitabine [6] or FOLFIRINOX [7], were associated with a survival advantage. We acknowledge the fact that the chemotherapy regimens adopted in our study were diverse, e.g., the proportion of tegafur or S-1 was relatively higher in the chemotherapy group than in the combination group. S-1 is an oral drug composed of tegafur, gimestat, and oteracil potassium [28], and S-1 monotherapy has been shown to be less toxic and well tolerable in PC [29]. The GEST study indicated that S-1 was non-inferior to gemcitabine and that adding S-1 did not significantly improve the survival time compared to gemcitabine alone in PC patients [29]. A phase II trial of adjuvant chemotherapy revealed that tegafur/uracil and gemcitabine provided similar efficacy to gemcitabine alone in resected PC patients [30]. A meta-analysis evaluating 12 different chemotherapeutic regimens revealed that except for FOLFIRINOX or gemcitabine monotherapy, the rest of the chemotherapy regimens, such as gemcitabine combined with S-1 (tegafur) or nab-paclitaxel, have similar efficacies [31]. Thus, it is unlikely that the heterogeneous chemotherapy regimens have significantly affected patients' outcomes.

Currently, some oncologists believe that chemotherapy induces an immunosuppressive microenvironment. Although there is no direct evidence showing immunosuppression by chemotherapy, a previous publication indicated that the immune system could be reset by re-obtaining various immune cell subsets [32]. In addition, several observations have indicated that despite their immunosuppressive effects, some conventional chemotherapeutic agents rely on cancer cell-extrinsic molecular and cellular cascades to stimulate antitumour immunity [33]. For example, gemcitabine is one of the standard chemotherapy regimens for PC, and previous research has proven that it not only promotes the apoptosis of tumor cells to increase antigen presentation [34] but also elicits naive T-cell activation to reverse the immunosuppressive microenvironment [35]. Paclitaxel may be a particularly strong immunostimulant, because it is able to both activate $CD8^+$ T cells and suppress immunosuppressive cells, such as regulatory T cells [36]. As the mechanisms of chemotherapeutic drugs are diverse, combining chemotherapies of different classes might maximize the clinical benefits. Thus, immunotherapy plus a doublet chemotherapy may be a preferable treatment regimen for PC.

The safety profile of ICIs combined with chemotherapy observed in this study was consistent with that seen previously for the treatment of other tumor types and advanced PC. The Keynote-189 trial showed that the incidence rates of grade 3 or higher TRAEs were similar between the pembrolizumab plus chemotherapy group and the placebo plus chemotherapy group (67.2% vs 65.8%) [37]. The results from a clinical study on pembrolizumab, gemcitabine, and nab-paclitaxel in metastatic PC indicated that grade 3 or higher events occurred in 53% of the patients and the most common adverse events were neutropenia (46.7%), thrombocytopenia (20%), hyponatremia (13.3%), AST elevation (6.7%), and ALT elevation (6.7%) [21]. In the current study, although the overall safety profile appeared to be worse with ICIs plus chemotherapy than with chemotherapy, the difference was not statistically significant and most immune-related adverse events were mild and controllable without any treatment interventions.

An important limitation of this study was the lack of patients receiving ICI monotherapy. Future studies should explore whether the addition of ICIs to chemotherapy also has greater efficacy than ICI monotherapy in these patients. In addition, although we prospectively designed the study, it was retrospective in nature. The small sample size might also have introduced selection bias and recall bias. Although these factors may have compromised the validity and reliability of the conclusions, the real-world data will still shed some light on the performance of ICIs plus chemotherapy in advanced PC and these results are worth further investigation in a prospective manner.

In conclusion, ICIs combined with chemotherapy are both efficacious and tolerable for patients with advanced PC. A doublet chemotherapy in conjunction with ICIs may be a preferable choice for those who are refractory to conventional therapy.

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Author contributions Conception and design: JXM, DYS, SLC and YH. Protocol writing: JXM, DYS, JS, SLC and YH. Data collection: CH, JLW, YYQ, GYC, XYL, PFC, JZ, WSD, SXC, ZZW, XZ and ZCY. Data analysis: JS, JXM and CG. Manuscript writing: JS, JXM, DYS and JLW. Manuscript revisions: CG, YH and SLC. All authors contributed to writing and reviewing the manuscript and approved the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval and ethical standards The study was approved by the institutional review board of the People's Liberation Army General Hospital, Beijing, China (approval number: S2018-144-02). This clinical study was conducted in accordance with the Helsinki declaration and its later amendments.

Informed consent Because of the retrospective nature of the study, informed consent was waived by the People's Liberation Army General Hospital, Beijing. This paper does not contain any individual person's data in any form.

References

1. Sun DY, Ma JX, Wang JL, Han C, Qian YY, Chen GY et al (2019) Anti-PD-1 therapy combined with chemotherapy in patients with advanced pancreas cancer in a real-world clinical setting. J Clin Oncol 37(15_suppl):e14103 **(Abstract)**
2. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics, 2018. CA Cancer J Clin 68:7–30
3. Gillen S, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J (2010) Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med 7:e1000267
4. van Roessel S, Kasumova GG, Verheij J, Najarian RM, Maggino L, de Pastena M, International validation of the eighth edition of the American Joint Committee on Cancer (AJCC) et al (2018) TNM staging system in patients with resected pancreatic cancer. JAMA Surg 153:183617
5. Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR et al (1997) Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol 15:2403–2413
6. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M et al (2013) Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 369:1691–1703
7. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y et al (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 364:1817–1825
8. Hammers H, Plimack ER, Infante JR, Ernstoff MS, Rini BI, McDermott DF et al (2014) Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma. Ann Oncol 25(suppl):iv361–iv362 **(abstr)**
9. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A et al (2016) Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 387:1909–1920
10. Heery CR, O'Sullivan-Coyne G, Madan RA, Cordes L, Rajan A, Rauckhorst M et al (2017) Avelumab for metastatic or locally advanced previously treated solid tumors (JAVELIN Solid Tumor): a phase 1a, multicohort, dose-escalation trial. Lancet Oncol 18:587–598
11. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD et al (2015) PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 372:2509–2520
12. Humphris JL, Patch AM, Nones K, Bailey PJ, Johns AL, McKay S et al (2017) Hypermutation in pancreatic cancer. Gastroenterology 152:68–74
13. Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS et al (2014) Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 515:563–567
14. Patnaik A, Kang SP, Rasco D, Papadopoulos KP, Elassaiss-Schaap J, Beeram M et al (2015) Phase I study of pembrolizumab (MK-3475; Anti-PD-1 Monoclonal Antibody) in patients with advanced solid tumors. Clin Cancer Res 21:4286–4293
15. Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US et al (2010) Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother 33:828–833
16. Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV et al (2013) Signatures of mutational processes in human cancer. Nature 500:415–442
17. Vonderheide RH, Bayne LJ (2013) Inflammatory networks and immune surveillance of pancreatic carcinoma. Curr Opin Immunol 25:200–205
18. Winograd R, Byrne KT, Evans RA, Odorizzi PM, Meyer AR, Bajor DL et al (2015) Induction of T-cell immunity overcomes complete resistance to PD-1 and CTLA-4 blockade and improves survival in pancreatic carcinoma. Cancer Immunol Res 3:399–411
19. Zitvogel L, Galluzzi L, Smyth MJ, Kroemer G (2013) Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. Immunity 39:74–88
20. Smyth MJ, Ngiow SF, Ribas A, Teng MW (2016) Combination cancer immunotherapies tailored to the tumour microenvironment. Nat Rev Clin Oncol 13:143–158

21. Weiss GJ, Blaydorn L, Beck J, Bornemann-Kolatzki K, Urnovitz H, Schütz E et al (2018) Phase Ib/II study of gemcitabine, nab-paclitaxel, and pembrolizumab in metastatic pancreatic adenocarcinoma. Investig New Drugs 36:96–102
22. Borazanci EH, Jameson GS, Board MJ, Ramanathan RK, Korn RL, Caldwell L et al (2018) A phase II pilot trial of nivolumab (N) + albumin bound paclitaxel (AP) + paricalcitol (P) + cisplatin (C) + gemcitabine (G) (NAPPCG) in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (PDAC). J Clin Oncol 36(4suppl):abstract358
23. Renouf DJ, Dhani NC, Kavan P, Jonker DJ, Wei ACC, Hsu T et al (2018) The Canadian Cancer Trials Group PA.7 trial: results from the safety run in of a randomized phase II study of gemcitabine (GEM) and nab-paclitaxel (Nab-P) versus GEM, nab-P, durvalumab (D), and tremelimumab (T) as first-line therapy in metastatic pancreatic ductal adenocarcinoma (mPDAC). J Clin Oncol 36(4suppl):abstract349
24. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
25. Chen AP, Setser A, Anadkat MJ, Cotliar J, Olsen EA, Garden BC et al (2012) Grading dermatologic adverse events of cancer treatments: The Common Terminology Criteria for Adverse Events Version 4.0. J AM Acad Dermatol 67:1025–1039
26. Des Jarlais DC, Lyles C, Crepaz N, TREND Group (2005) Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: the TREND statement. Am J Public Health 94:361–366
27. Di Marco M, Di Cicilia R, Macchini M, Nobili E, Vecchiarelli S, Brandi G et al (2010) Metastatic pancreatic cancer: is gemcitabine still the best standard treatment? (Review). Oncol Rep 23:1183–1192
28. Shirasaka T, Shimamoto Y, Ohshimo H, Yamaguchi M, Kato T, Yonekura K et al (1996) Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation of the tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. Anticancer Drugs 7:548–557
29. Ueno H, Ioka T, Ikeda M, Ohkawa S, Yanagimoto H, Boku N et al (2013) Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. J Clin Oncol 31:1640–1648
30. Yoshitomi H, Togawa A, Kimura F, Ito H, Shimizu H, Yoshidome H et al (2008) A randomized phase II trial of adjuvant chemotherapy with uracil/tegafur and gemcitabine versus gemcitabine alone in patients with resected pancreatic cancer. Cancer 113:2448–2456
31. Zhang SH, Liu GF, Li XF, Liu L, Yu SN (2018) Efficacy of different chemotherapy regimens in treatment of advanced or metastatic pancreatic cancer: a network meta-analysis. J Cell Physiol 233:3352–3374
32. Bracci L, Schiavoni G, Sistigu A, Belardelli F (2014) Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. Cell Death Differ 21:15–25
33. Galluzzi L, Senovilla L, Zitvogel L, Kroemer G (2012) The secret ally: immunostimulation by anticancer drugs. Nat Rev Drug Discov 11:215–233
34. Nowak AK, Lake RA, Marzo AL, Scott B, Heath WR, Collins EJ et al (2003) Induction of tumor cell apoptosis in vivo increases tumor antigen cross-presentation, cross-priming rather than cross-tolerizing host tumor-specific CD8 T cells. J Immunol 170:4013–4905
35. Plate JM, Plate AE, Shott S, Bograd S, Harris JE (2005) Effect of gemcitabine on immune cells in subjects with adenocarcinoma of the pancreas. Cancer Immunol Immunother 54:915–925
36. Soliman HH (2016) Nab-Paclitaxel as a potential partner with checkpoint inhibitors in solid tumors. Onco Targets Ther 10:101–112
37. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F et al (2018) Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 378:2078–2092

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