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Contents

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Contents

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ORIGINAL ARTICLE

Retrospective Study

Programmed cell death 1 inhibitor sintilimab plus concurrent chemoradiotherapy for locally advanced pancreatic adenocarcinoma

Shi-Qiong Zhou, Peng Wan, Sen Zhang, Yuan Ren, Hong-Tao Li, Qing-Hua Ke

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Abstract

BACKGROUND

Pancreatic adenocarcinoma, a malignancy that arises in the cells of the pancreas, is a devastating disease with unclear etiology and often poor prognosis. Locally advanced pancreatic cancer, a stage where the tumor has grown significantly but has not yet spread to distant organs, presents unique challenges in treatment. This article aims to discuss the current strategies, challenges, and future directions in the management of locally advanced pancreatic adenocarcinoma (LAPC).

AIM

To investigate the feasibility and efficacy of programmed cell death 1 (PD-1) inhibitor sintilimab plus concurrent chemoradiotherapy for LAPC.

METHODS

Eligible patients had LAPC, an Eastern cooperative oncology group performance status of 0 or 1, adequate organ and marrow functions, and no prior anticancer therapy. In the observation group, participants received intravenous sintilimab 200 mg once every 3 wk, and received concurrent chemoradiotherapy (concurrent conventional fractionated radiotherapy with doses planning target volume 50.4 Gy and gross tumor volume 60 Gy in 28 fractions and oral S-1 40 mg/m^2 twice daily on days 1-14 of a 21-d cycle and intravenous gemcitabine 1000 mg/m^2 on days 1 and 8 of a 21-d cycle for eight cycles until disease progression, death, or unacceptable toxicity). In the control group, participants only received concurrent chemoradiotherapy. From April 2020 to November 2021, 64 participants were finally enrolled with 34 in the observation group and 30 in the control group.

RESULTS
Thirty-four patients completed the scheduled course of chemoradiotherapy, while 32 (94.1%) received sintilimab plus concurrent chemoradiotherapy with 2 patients discontinuing sintilimab in the observation group. Thirty patients completed the scheduled course of chemoradiotherapy in the control group. Based on the Response Evaluation Criteria in Solid Tumors guidelines, the analysis of the observation group revealed that a partial response was observed in 11 patients (32.4%), stable disease was evident in 19 patients (55.9%), and 4 patients (11.8%) experienced progressive disease; a partial response was observed in 6 (20.0%) patients, stable disease in 18 (60%), and progressive disease in 6 (20%) in the control group. The major toxic effects were leukopenia and nausea. The incidence of severe adverse events (AEs) (grade 3 or 4) was 26.5% (9/34) in the observation group and 23.3% (7/30) in the control group. There were no treatment-related deaths. The observation group demonstrated a significantly longer median overall survival (22.1 mo compared to 15.8 mo) ($P < 0.05$) and progression-free survival (12.2 mo *vs* 10.1 mo) ($P < 0.05$) in comparison to the control group. The occurrence of severe AEs did not exhibit a statistically significant difference between the observation group and the control group ($P > 0.05$).

CONCLUSION
Sintilimab plus concurrent chemoradiotherapy was effective and safe for LAPC patients, and warrants further investigation.

Key Words: Immunotherapy; Concurrent chemoradiotherapy; Locally advanced pancreatic adenocarcinoma; Programmed cell death 1; Sintilimab

Core Tip: The article presents an insightful exploration of a study of the combination of sintilimab with S-1 and gemcitabine concurrent radiotherapy for locally advanced pancreatic cancer (LAPC). The observation group had significantly longer median progression-free survival and overall survival than the control group. The occurrence of severe adverse events did not exhibit a statistically significant difference between the observation group and the control group, with a *P* value greater than 0.05. It is considered a promising, effective, and well-tolerated treatment for LAPC.

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INTRODUCTION

The prognosis of patients with locally advanced pancreatic cancer (LAPC) remains extremely poor and, in most historical studies, the median survival duration typically falls within a range of 8 to 12 mo. However, the 5-year overall survival (OS) rate remains relatively low, hovering at approximately 9%[1].

Currently, the treatment of LAPC is multidisciplinary, often combining surgical resection, chemotherapy, and radiation therapy. Surgical resection, known as pancreatoduodenectomy or Whipple procedure, is the preferred approach for patients with resectable tumors. However, most patients present with locally advanced disease that is not amenable to surgical resection due to tumor invasion of surrounding structures or metastasis[2].

In such cases, chemotherapy plays a crucial role. The most commonly used chemotherapeutic agents include gemcitabine, fluorouracil, and platinum-based drugs. These agents are administered either as monotherapy or in combination to achieve synergistic antitumor effects. Chemotherapy is typically administered before surgery to shrink the tumor and increase the chances of successful resection (neoadjuvant therapy), or after surgery to eliminate residual cancer cells (adjuvant therapy).

Radiation therapy, either alone or combined with chemotherapy, is also used to treat LAPC. This procedure involves the utilization of high-energy radiation to effectively eliminate cancerous cells and reduce the size of the tumor. Advanced techniques such as stereotactic body radiation therapy and intensity-modulated radiation therapy (IMRT) allow for more precise delivery of radiation to the tumor while minimizing damage to surrounding healthy tissue.

Despite these advancements, locally advanced pancreatic adenocarcinoma remains a challenging disease to treat. The prognosis for patients with this condition is often poor, with limited survival rates. This is partly due to the aggressive nature of the cancer and its resistance to traditional treatment modalities.

Moreover, the complex anatomy of the pancreas and its close proximity to vital structures make surgical resection challenging. Even with resection, the risk of recurrence and metastasis remains high. Additionally, the side effects of chemotherapy and radiation therapy can be significant, further compromising the quality of life for patients.

To address these challenges, researchers are exploring novel treatment strategies. A promising avenue lies in the advancement of targeted therapies, which are designed to specifically target and eliminate cancer cells while minimizing collateral damage to healthy cells. These therapies, including immunotherapy and gene-based therapies, are in various stages of clinical development and show promise in improving outcomes for patients with LAPC[3-5].

Treatment options specifically for patients with LAPC are scarce and chemotherapy or radiotherapy alone delivers limited efficacy. Twenty percent of patients undergoing initial chemoradiation therapy unexpectedly exhibited immediate metastases following treatment[6,7], and in some cases, they even suffer from higher toxicity levels compared to those who solely receive chemotherapy. Recent Phase 2/3 studies have demonstrated a notable increase in median survival rates through the utilization of programmed cell death 1 (PD-1) inhibitors, providing promising results in the field of cancer treatment. PD-1 inhibitor sintilimab, a human IgG4 monoclonal antibody, has shown efficacy in liver cancer, non-small cell lung cancer, classical Hodgkin's lymphoma, rectal cancer, and cervical cancer[8-12].

Immunotherapy and radiotherapy are promising therapeutic options for LAPC, and they have the potential to enhance the effects of chemotherapy when used in combination. Therefore, in this retrospective study, we aimed to comprehensively assess and compare the efficacy and safety profile of the PD-1 inhibitor, sintilimab, combined with S-1 plus gemcitabine concurrent chemoradiotherapy *vs* S-1 plus gemcitabine concurrent chemoradiotherapy in the treatment of LAPC.

MATERIALS AND METHODS

Patient eligibility

We enrolled patients aged 18-80 years whose estimated life expectancy was 12 wk. The patients had been confirmed histologically or cytologically to have unresectable LAPC. The inclusion criteria were as follows: Eastern cooperative oncology group performance status of 0 or 1; no earlier treatment for pancreatic cancer; no evidence of distant metastasis; adequate hematological function; adequate hepatic and renal function; adequate oral intake; and written informed consent. Exclusion criteria were as follows: active infection; watery diarrhea; active gastroduodenal ulcers; pleural effusion or ascites; complications such as history of drug hypersensitivity, active concomitant malignancy, heart disease or renal disease; mental disorders; pregnant and lactating women; and women of childbearing age unless using effective contraception.

For pretreatment staging, thoracic and abdominal computed tomography (CT) was needed to exclude the presence of distant metastasis and to assess local extension of the tumor. Tumor unresectability criteria included tumor encasement of the superior mesenteric artery, bilateral portal vein, common hepatic artery, or celiac trunk. Before treatment, all patients with obstructive jaundice underwent percutaneous transhepatic or an endoscopic retrograde biliary drainage.

Characteristics of patients

From April 2020 to November 2021, a total of 64 patients participated in the study conducted at the First Affiliated Hospital of Yangtze University, located in Jingzhou, China. The comprehensive characteristics of these patients have been comprehensively outlined in Table 1 for a clear and detailed understanding. Sixty-four participants were finally enrolled with 34 in the observation group and 30 in the control group. There was no significant difference in any baseline characteristics between these two groups (Table 1). All patients were thoroughly briefed on the pros and cons of both treatment options, including potential outcomes, morbidity associated with treatment, as well as financial implications. Consequently, the ultimate decision regarding their treatment was primarily made by each patient.

Treatment schedule

In the observation group, participants received intravenous sintilimab 200 mg once every 3 wk, and concurrent chemoradiotherapy [concurrent conventional fractionated radiotherapy with doses planning target volume (PTV) 50.4 Gy and gross tumor volume (GTV) 60 Gy in 28 fractions and oral S-1 40 mg/m^2 twice daily on days 1-14 of a 21-d cycle, and intravenous gemcitabine 1000 mg/m^2 on days 1 and 8 of a 21-d cycle for eight cycles until disease progression, death, or unacceptable toxicity]. In the control group, participants received only concurrent chemoradiotherapy (concurrent conventional fractionated radiotherapy with doses PTV 50.4 Gy and GTV 60 Gy in 28 fractions and oral S-1 40 mg/m^2 twice daily on days 1-14 of a 21-d cycle and intravenous gemcitabine 1000 mg/m^2 on days 1 and 8 of a 21-d cycle for eight cycles until disease progression, death, or unacceptable toxicity).

IMRT was precisely administered through three-dimensional (3D) treatment planning, utilizing 15 MV photons for optimal precision. The overall dosage consisted of 50.4 Gy targeted to the PTV and 60 Gy delivered to the GTV, distributed across 28 fractions over approximately 5.5 wk. This approach ensured a controlled and effective administration of radiation therapy. The GTV was delineated as the region of solid, macroscopic tumor tissue that exhibited contrast enhancement on CT and magnetic resonance imaging (MRI), and/or positron emission tomography. The clinical target volume (CTV) was defined as encompassing the GTV with an additional margin of at least 5 mm, considering any potential areas of microscopic tumor spread as well as the involved regional lymph nodes. The CTV, inclusive of a 5-mm lateral margin to compensate for potential inaccuracies, and a 10-mm craniocaudal margin to account for daily set-up errors and respiratory organ motion, was collectively designated as the PTV. Not more than 30% of the total volume received ≥ 18 Gy in both kidneys. If only one kidney was functional, not more than 10% of the total volume received ≥ 18 Gy, and the liver mean dose was limited to ≤ 30 Gy. The stomach received a maximum dose of ≤ 55 Gy, and not more than 30% of the volume received 45-55 Gy. The dosage delivered to the spinal cord was consistently kept below 45 Gy, ensuring safety and precision throughout the treatment process.

Table 1 Patient characteristics

Feature	Observation group	Control group
Age in yr		
Median	57	55
Range	18-70	49-80
Sex		
Male	20	16
Female	14	14
Performance status		
0	29	28
1	5	2
Stage		
Stage A	21	17
Stage B	13	13

Evaluation

All incoming patients were comprehensively included in both response and toxicity assessments. Throughout the chemotherapy process, thorough physical examinations, biochemistry tests, and complete blood cell counts were meticulously evaluated on both the first and eighth days of each treatment cycle. In accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, an objective assessment of tumor response was conducted every 4 to 6 wk utilizing CT or MRI. Additionally, the levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were monitored at the same frequency to track any potential changes. To confirm the objective response, the patient status was evaluated at an interval of no less than 4 wk, with complete response (CR), partial response (PR), and stable disease being the criteria used for assessment. The duration of the response was determined by measuring the time interval between the initial documentation of a clinical response (either CR or PR) and the subsequent documentation of tumor progression. This period provides a quantitative assessment of the treatment's effectiveness in maintaining a favorable outcome before disease progression occurs. Adverse events (AEs) were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Objective responses and AEs were confirmed by an external review committee. The progression-free survival (PFS) was determined by calculating the duration from the initiation of treatment to the occurrence of either documented disease progression or death from any cause. The date of treatment initiation to the censored date of follow-up or death was calculated as OS.

RESULTS

Efficacy

Thirty-four patients completed the scheduled course of chemoradiotherapy, while 32 (94.1%) received sintilimab plus concurrent chemoradiotherapy, with 2 patients discontinuing sintilimab in the observation group. Thirty patients completed the scheduled course of chemoradiotherapy in the control group. The objective response rate (ORR), as determined by the RECIST 1.0 criteria, stood at 32.4% in the observation group, significantly higher than the 20.0% observed in the control group. Similarly, when assessing the disease control rate (DCR) utilizing the RECIST 1.0 criteria, the observation group demonstrated a significant achievement of 88.2%, representing a noteworthy enhancement in comparison to the 80.0% observed in the control group. The observation group underwent a median follow-up duration of 16.3 mo, varying between 12.2 and 26.5 mo. In contrast, the control group exhibited a median follow-up period of 17.4 mo, spanning from 15.1 to 25.6 mo. The median OS for the observation group was 22.1 mo, with a 95%CI extending from 16.3 to 27.6 mo. In contrast, the control group demonstrated a median OS of 15.8 mo, accompanied by a 95%CI varying from 5.5 to 18.3 mo. This comparison clearly highlights the disparities in survival outcomes between the two groups. This difference was statistically significant ($P < 0.05$; Table 2). The median PFS in the observation group was 12.2 mo (95%CI: 5.5-18.3 mo), whereas in the control group, it was 10.1 mo (95%CI: 5.8-14.2 mo) ($P < 0.05$; Table 2). Detailed univariable and multivariable analyses revealed that the sole independent prognostic factor significantly influencing both OS [hazard ratio (HR) = 0.484; 95%CI: 0.245-0.948; $P < 0.05$] and PFS (HR = 0.579; 95%CI: 0.334-0.991; $P < 0.05$; Table 2) was the allocation of treatment. During the follow-up phase, it was observed that there was no notable variation in the occurrence of treatment failure or the need for post-protocol intervention among the two groups.

Adverse events

Table 3 presents a comprehensive overview of Grade 1-4 AEs. Notably, no unexpected toxicities were observed

Table 2 Summary of tumor response and survival outcomes according to Response Evaluation Criteria in Solid Tumors 1.0 criteria

Outcomes	Observation group, *n* = 34	Control group, *n* = 30	*P* value
Best tumor response			
Complete response	0 (0)	0 (0)	
Partial response	11 (32.4)	6 (20.0)	
Stable disease	19 (55.9)	18 (60.0)	
Progressive disease	4 (11.8)	6 (20)	
Objective response rate	11 (32.4)	6 (20)	
Disease control rate	30 (88.2)	24 (80)	
Median OS in month	22.1 ± 2.6 (16.3-27.6)	17.8 ± 2.3 (12.9-22.8)	< 0.05
Median PFS in month	12.2 ± 3.1 (5.5-18.3)	10.1 ± 2.2 (5.8-14.2)	< 0.05

[1]Data are *n* (%) or mean ± standard deviation (95% confidence interval).
OS: Overall survival; PFS: Progression-free survival.

Table 3 Toxicity

Symptom	Control group, No. of patients				Observation group, No. of patients			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	11	7	3	1	12	8	4	1
Fatigue	15	6	2	0	16	9	2	0
Anemia	14	5	1	0	15	6	1	0
Nausea	18	8	0	0	20	10	1	0
Anorexia	8	5	0	0	11	7	0	0

throughout the study period, indicating a favorable safety profile. Furthermore, there were no fatalities attributed to the treatment administered, underscoring its tolerability. The occurrence of severe AEs is also detailed in the table, providing crucial insights into the potential risks associated with the treatment. Grade 3 or 4 was 26.5% (9/34) in the observation group and 23.3% (7/30) in the control group. In the observation group, the most frequent (≥ 10% incidence) Grade 3 AEs were leukopenia (*n* = 5; 14.7%), fatigue (*n* = 2; 5.9%), and anemia (*n* = 1; 2.9%). In the control group, the most frequent AEs were leukopenia (*n* = 4; 13.3%), fatigue (*n* = 2; 6.7%), and anemia (*n* = 1; 3.3%).

DISCUSSION

LAPC has a poor prognosis and is one of the most lethal cancers globally[1]. Optimizing patient selection is imperative to strike a balance between disease control, toxicity management, and the maintenance of a high quality of life, because many patients with LAPC are not curable through multidisciplinary treatment[13]. Research has demonstrated that the use of 3D conformal radiotherapy, IMRT, or stereotactic body radiotherapy, combined with concurrent chemotherapy, effectively controls local disease progression. This combined approach has been shown to not only prevent the development of metastatic disease but also significantly enhance survival rates when compared to chemotherapy alone [14-18]. However, the effect is limited, and many patients with LAPC who received upfront chemoradiotherapy experienced metastases soon after they completed therapy.

Immunotherapy, which harnesses the power of the immune system to attack cancer cells, is a particularly exciting area of research. Clinical trials are underway to evaluate the efficacy of immunotherapy agents, such as immune checkpoint inhibitors, in combination with chemotherapy and/or radiation therapy for the treatment of LAPC.

Gene-based therapies, such as CRISPR-Cas9 gene editing and oncogenic virus-based therapies, are also being explored as potential treatment options. These therapies aim to correct genetic mutations that drive cancer growth or activate the immune system to target cancer cells more effectively.

Moreover, the development of personalized medicine approaches based on tumor genomics and proteomics is expected to improve treatment outcomes. By understanding the unique genetic and molecular characteristics of each patient's tumor, doctors can tailor treatment plans that are more likely to be effective and less likely to cause adverse side effects.

LAPC remains a significant challenge in oncology. However, with ongoing research and the development of novel treatment strategies, we are hopeful that the prognosis for these patients will improve in the future. A multifaceted approach, combining surgical resection, chemotherapy, radiation therapy, and novel therapeutic strategies, is likely to be the key to overcoming this devastating disease[19-23].

In recent years, there has been intensive research on checkpoint inhibitor immunotherapy for LAPC[24-27]. Anti-PD-1 immunotherapy holds the potential to effectively collaborate with radiotherapy, leveraging immunogenic cell death to enhance T-cell priming and reversing the immunosuppressive microenvironment, thereby fostering a synergistic therapeutic effect[28,29]. Chen *et al*[30] demonstrated encouraging results in their study: the combination of nab-paclitaxel and gemcitabine, along with the PD-1 inhibitor camrelizumab and radiotherapy, exhibited both efficacy and safety in treating patients with LAPC. This integrated approach led to a notable extension of the median OS to 22.3 mo, which was significantly higher than the 18.6 mo observed in the control group ($P < 0.05$). This demonstrates the effectiveness of our comprehensive strategy in prolonging survival rates, and similarly improved the median PFS to 12.0 mo, *vs* 10.5 mo in the comparator arm ($P < 0.05$). It has been reported that, in combination with chemotherapy, this exhibits a synergistic effect, leading to a reduction in tumor burden by mitigating chemotherapy resistance and modifying the microenvironment[31-34]. Therefore, there is a compelling rationale for combining these three therapies to effectively improve both local and systemic tumor control. However, it is noteworthy that there is a significant lack of clinical data specifically addressing this aspect.

Accordingly, we conducted a retrospective study aimed at comprehensively evaluating and contrasting the therapeutic efficacy and safety profile of S-1 plus gemcitabine chemoradiotherapy administered alongside anti-PD-1 immunotherapy (sintilimab) with the standard treatment of S-1 plus gemcitabine chemoradiotherapy alone in patients suffering from LAPC. Based on the RECIST 1.0 criteria, the ORR was calculated to be 32.4% in the observation group, whereas it was lower, at 20.0%, in the control group. While the DCR achieved in the observation group, utilizing the RECIST 1.0 criteria, stood at an impressive 88.2%, it was slightly lower in the control group, registering a rate of 80.0%. The median OS for patients in the observation group was 22.1 mo, significantly longer than the 15.8 mo observed in the control group ($P < 0.05$). Median PFS was 12.2 mo in the observation group and 10.1 mo in the control group ($P < 0.05$). Univariate and multivariate analyses revealed that the sole independent prognostic factor for both OS and PFS was the allocation of treatment. Notably, during the follow-up period, no statistically significant disparities were observed in terms of the patterns of treatment failure or post-protocol interventions among the two groups. No unexpected toxicity was detected, and there were no fatalities attributed to the treatment. The occurrence of severe AEs did not exhibit a statistically significant difference between the two groups, with rates of 26.5% and 23.3%, respectively. In the observation group, the most prevalent Grade ≥ 3 AEs occurring at a frequency of ≥ 10% were leukopenia (accounting for 14.7% of cases), fatigue (5.9%), and anemia (2.9%). When compared to the control group, these rates were comparable, with leukopenia occurring in 13.3% of cases, fatigue in 6.7%, and anemia in 3.3%.

CONCLUSION

In conclusion, our study demonstrates for the first time that the combination of S-1 and gemcitabine chemoradiotherapy, coupled with anti-PD-1 immunotherapy (sintilimab), exhibits both efficacy and safety in patients with LAPC. This finding holds promise for future exploration and investigation.

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FOOTNOTES

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