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ORIGINAL ARTICLE

Retrospective Study

Recent efficacy and long-term survival of *Astragalus* polysaccharide combined with gemcitabine and S-1 in pancreatic cancer

Guang-Yu Li, Jing Jiang

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Abstract

BACKGROUND

Pancreatic cancer is a highly malignant tumor with a rapid progression rate and a high susceptibility to infiltration and metastasis. *Astragalus* polysaccharide (APS), a pure Chinese medicine preparation primarily made from the traditional Chinese herb *Astragalus*, plays a positive role in the treatment of many malignant tumors.

AIM

To explore the recent efficacy of APS combined with gemcitabine plus tegafur gimeracil oteracil potassium capsule (S-1) (GS) regimen in the treatment of pancreatic cancer and assess its effect on the immune function and long-term survival of patients.

METHODS

A total of 97 patients who were diagnosed with pancreatic cancer and received GS chemotherapy at The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine) from March 2021 to December 2021 were included in the retrospective analysis. Among them, 41 patients received APS combined with GS chemotherapy, and 56 patients received GS chemotherapy only. The recent efficacy, immune function, adverse reactions, and long-term survival were compared among these patients.

RESULTS

After 4 cycles of treatment, the objective response rate of patients receiving the combined therapy of APS and GS was 51.22%, and the disease control rate (DCR) was 56.10%, higher than those of patients receiving the monotherapy with GS alone (30.36% and 35.71%, respectively). Besides, the percentages of CD3+ T cells

(50.18% ± 9.57%) and CD4+ T cells (31.52% ± 5.33%) in the peripheral blood of patients receiving the combined therapy of APS and GS were higher compared with those treated with GS regimen alone [(44.06% ± 8.55%) and (26.01% ± 7.83%), respectively]. Additionally, the incidences of leukopenia, thrombocytopenia, and fatigue in patients receiving the combined therapy of APS and GS were significantly lower than those in patients receiving the monotherapy of GS alone (17.07%, 9.76%, 31.71% *vs* 37.50%, 28.57%, 60.71%). Moreover, the median survival time of patients receiving the combined therapy of APS and GS was 394 days, significantly longer than that of patients receiving the mono-therapy of GS alone (339 days) (hazard ratio: 0.66; 95%CI: 0.45-0.99; $P = 0.036$). All these differences were statistically si-gnificant ($P < 0.05$).

CONCLUSION

The combined therapy of APS and GS improved the recent efficacy and long-term survival of patients with pancreatic cancer and alleviated chemotherapy-induced immune suppression and adverse reactions.

Key Words: Pancreatic cancer; *Astragalus* polysaccharide; Long-term survival; Immune function; Traditional Chinese medicine

Core Tip: *Astragalus* polysaccharide (APS) plays an active role in the treatment of malignant tumors based on traditional Chinese medicine (TCM). This study analyzed the effects of the combined therapy of APS and gemcitabine plus tegafur gimeracil oteracil potassium capsule (S-1) in the treatment of pancreatic cancer, showing improved objective response rate and disease control rate, increased CD4+ T cells and serum interleukin-2 levels, and prolonged median survival time. The findings demonstrated the potential of APS as an effective TCM-based treatment option in pancreatic cancer therapies.

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INTRODUCTION

Pancreatic cancer is a highly malignant tumor with a rapid progression rate and a high susceptibility to infiltration and metastasis. Patients with pancreatic cancer may progress to advanced stages over time, and they may present with gastrointestinal bleeding or abdominal pain due to the insidious onset and atypical early symptoms of this cancer. Consequently, many patients with pancreatic cancer miss the opportunity for surgery, leading to high recurrence and metastasis rates even after radical surgery[1]. Pancreatic cancer patients can receive palliative treatments like chemotherapy or supportive surgery to extend their survival. Currently, the common frontline drugs for the treatment of this cancer include paclitaxel, gemcitabine, S-1, and 5-fluorouracil[2]. However, the overall efficacy of pancreatic cancer treatment is not satisfactory due to such factors as drug resistance and toxic side effects of chemotherapy drugs. Therefore, there is an urgent demand for enhancing the efficacy of chemotherapy and reducing its toxic side effects in clinical studies.

Astragalus polysaccharide (APS), a pure Chinese medicine preparation primarily made from the traditional Chinese herb *Astragalus*, plays a positive role in the treatment of many malignant tumors[3]. APS is identified as a heteropolysaccharide[4], and it is mainly composed of glucose, arabinose, xylose, mannose, and rhamnose[5]. As revealed in studies on its primary structure, the main chain has a 1,3-linked-β-D-Gal residue, and its branches contain multiple monosaccharide residues, mainly comprising β-Glc, 1,6-linked-α-Gal, 1,5-linked-β-Xyl, 1,4-linked-β-Gal, β-D-Gal, 1,2-linked-α-Rha, and 1,2,4-linked-α-Rha[6]. The molecular weight, content of glucuronic acid, glycobase composition, and different glycosidic bonds significantly affect their biological activities[7]. In the experiments based on BALB/c mice grafted by H22 hepatocarcinoma, APS increased the thymus and spleen indices and limited the solid tumor growth. Besides, APS also increased the serum lymphokine levels of interleukin (IL)-2, IL-12, and Tumor necrosis factor α (TNF-α), but lowered the level of IL-10[8-10]. In addition, APS down-regulated the mRNA level of MDR1 and P-GP pump activities and enhanced the sensitivity of Adriamycin-resistant H22 cells to chemotherapy[11]. Furthermore, by activating apoptosis-related genes and the JNK pathway, APS improved the sensitivity of SKOV3 ovarian-carcinoma cells to cisplatin[12]. APS may also reduce the PD-L1-mediated immunosuppression of Treg cells *via* the miR-133a-3p/MSN axis, thus decreasing FOXp3 mRNA production[13,14].

This may be the first scientific attempt to explore the short-term efficacy, immune function, and long-term survival impact of APS combined with gemcitabine and S-1 (GS) regimen for the treatment of pancreatic cancer.

MATERIALS AND METHODS

General information

A retrospective study was conducted based on the patients diagnosed with pancreatic cancer and receiving GS chemotherapy at The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine) between March 2021 and December 2021. The inclusion criteria included: (1) Patients pathologically diagnosed with pancreatic cancer; (2) Patients with tumor-node-metastasis stages III-IV; (3) Patients receiving GS chemotherapy and completing four treatment cycles; (4) Patients with complete clinical and pathological data, including pre-treatment and post-treatment peripheral venous blood test data in the medical information system; and (5) Patients with complete follow-up data. The exclusion criteria included: (1) Patients with a history of other malignant tumors; or (2) Patients previously receiving anti-tumor treatments such as radiotherapy, chemotherapy, or targeted therapy before our GS chemotherapy. A total of 97 patients were included in the retrospective study. Among them, 41 patients received APS injection combined with GS chemotherapy, and 56 patients received GS chemotherapy only. All patients completed four treatment cycles. The comparison of clinical data between the patients showed no statistically significant differences ($P > 0.05$), as shown in Table 1. This study was approved by the Ethics Committee of Zhejiang Provincial Hospital of Chinese Medicine (Ethics No. 2024-KLS-266-02).

APS administration and GS regimen

The GS chemotherapy was implemented according to the "2020 Guidelines of Chinese Society of Clinical Oncology": Gemcitabine 1000 mg/m^2, intravenous infusion on days 1 and 8; oral administration of S-1 60-100 mg twice daily on days 1-14, with a 3-week cycle. In addition to GS chemotherapy, APS injection (Tianjin Sainuo Pharmaceutical Co., Ltd.) was given to patients in necessity after the GS chemotherapy. On days 1-7 of the chemotherapy cycle, APS injection (250 mg) was added to 500 mL of saline solution for intravenous infusion once a day following the drug instruction.

Observational indices

Short-term efficacy: Short-term efficacy was evaluated after four treatment cycles according to the Response Evaluation Criteria in Solid Tumours: Revised RECIST guideline (version 1.1)[15], including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The overall response rate (ORR) was calculated as CR + PR, and the disease control rate (DCR) was calculated as CR + PR + SD.

Hematology, biochemistry, and immunological functions: The peripheral venous blood of patients with pancreatic cancer was collected during their hospitalization for disease evaluation after chemotherapy as necessary. All hemanalyses were performed by the Clinical laboratory in The First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Provincial Hospital of Chinese Medicine). In this retrospective study, all data were extracted from the medical information system, which was approved by the Ethics Committee of Zhejiang Provincial Hospital of Chinese Medicine (Ethics No. 2024-KLS-266-02).

Adverse reactions and traditional Chinese medicine (TCM) syndrome score observation: The regular monitoring of blood routine examination and liver functions after chemotherapy was conducted to observe the incidence of leukopenia, thrombocytopenia, and liver function impairment. The observation of TCM syndromes such as fatigue, thick and greasy tongue coating, and weak pulse was scored as follows: No obvious symptoms (0 points), mild symptoms (2 points), moderate symptoms (4 points), and severe symptoms (6 points). The syndrome assessment was conducted as per the TCM efficacy evaluation criteria[16]: Significant improvement: The TCM syndrome score decreased by more than 70%; some improvement: The TCM score decreased by 30%-69%; no improvement: The TCM syndrome score decreased by less than 30%.

Long-term survival: The long-term survival follow-up was conducted through outpatient visits, telephone calls, or online social media platforms. The follow-up content included overall survival (OS), which was defined as the time from the first day of chemotherapy to death or the last follow-up date. The follow-up was conducted monthly for the first 6 months, followed by every 3 months until May 2024. Statistical analysis was performed using SPSS 22.0 (SPSS, IBM, NY, United States). The *t*-test was performed for the comparison of continuous data among the patients, and the χ^2 test was performed for the comparison of count data. The Kaplan-Meier curve was plotted and the Log-rank test was conducted for the comparison of OS. $P < 0.05$ indicated statistical significance.

RESULTS

Comparison of short-term efficacy

The ORR and DCR of patients receiving the combined therapy of APS and GS were 51.22% and 56.10%, respectively, both significantly higher than those of patients receiving the monotherapy of GS alone (30.36% and 35.71%, respectively) after four cycles of chemotherapy. The difference was statistically significant ($P < 0.05$), as shown in Table 2.

Immune function

The patients receiving the combined therapy of APS and GS had higher percentages of CD3+ T cells, CD4+ T cells, CD4+/CD8+ T cell ratio, and serum IL-2 Level compared to the patients receiving the monotherapy of GS alone, with statistically significant differences ($P < 0.05$). The percentages of CD8+ T cells and serum INF-γ levels showed no statistically significant differences ($P > 0.05$), as shown in Table 3.

Table 1 Baseline information, *n* (%)

Indicators	Sex (male/female)	Age (year, mean ± SD)	TNM	
			IIB	III
APS + GS (n = 41)	24/17	60.10 ± 11.26	17 (41.16)	24 (58.54)
GS regimen (n = 56)	37/19	58.35 ± 10.36	22 (39.29)	34 (60.71)
χ^2 or t value	0.576	0.780	0.047	
P value	0.448	0.438	0.829	

APS: *Astragalus* polysaccharide; GS: Gemcitabine plus tegafur gimeracil oteracil potassium capsule (S-1); TNM: Tumor node metastasis classification.

Table 2 Comparison of short-term efficacy, *n* (%)

	ORR	DCR
APS + GS (n = 41)	21 (51.22)	23 (56.10)
GS regimen (n = 56)	17 (30.36)	20 (35.71)
χ^2 value	4.323	3.985
P value	0.038	0.046

APS: *Astragalus* polysaccharide; GS: Gemcitabine plus tegafur gimeracil oteracil potassium capsule (S-1); ORR: Overall response rate; DCR: Disease control rate.

Table 3 Immune function (%, mean ± SD)

Indicators	CD3+	CD4+	CD8+	CD4+/CD8+	IL-2 (pg/mL)	INF-γ (pg/mL)
APS + GS (n = 41)	50.18 ± 9.57	31.52 ± 5.33	18.65 ± 6.37	1.69 ± 0.21	3.30 ± 0.83	12.64 ± 4.90
GS regimen (n = 56)	44.06 ± 8.55	26.01 ± 7.83	18.06 ± 3.80	1.44 ± 0.21	2.67 ± 0.51	11.55 ± 3.70
t value	3.307	3.886	0.576	5.852	4.581	1.253
P value	0.001	0.000	0.566	0.000	0.000	0.213

APS: *Astragalus* polysaccharide; GS: Gemcitabine plus tegafur gimeracil oteracil potassium capsule (S-1); IFN-γ: Interferon-γ; IL-2: Interleukin-2.

Adverse reactions and TCM syndrome scores

Patients receiving the combined therapy of APS and GS had a lower incidence of leukopenia, thrombocytopenia, and liver function damage than those receiving the monotherapy of GS alone, with statistically significant differences (P < 0.05). The various scores of TCM symptoms in patients receiving the combined therapy of APS and GS decreased significantly (P < 0.05), as shown in Table 4.

Long-term survival

Kaplan-Meier curves of OS were plotted, and Log-rank tests were also conducted. The median survival time of patients receiving the combined therapy of APS and GS was 394 days, significantly longer than that of patients receiving the monotherapy of GS alone (339 days) (HR = 0.66; 95%CI: 0.45-0.99; P = 0.036), with statistically significant differences (P < 0.05), as shown in Figure 1.

DISCUSSION

TCM plays an important role in each stage of tumor occurrence and development by detoxification, tonifying deficiency, enhancing sensitivity to chemotherapy, reducing adverse reactions, and improving patient immunity, thereby improving the quality of life of patients[17,18]. According to the TCM theory, the occurrence of malignant tumors involves a process of righteousness deficiency and evil excess, with the deficiency of righteous Qi being an important pathogenesis of malignant tumors. Pancreatic cancer has an insidious onset and a high mortality rate, and most patients were diagnosed at an advanced stage, losing the chance for surgical procedures and requiring conservative chemotherapy. For elderly

Table 4 Adverse reactions and traditional Chinese medicine syndrome scores, *n* (%)

	Leukopenia	Thrombocytopenia	Liver function damage	Fatigue	Thick greasy tongue coating	Weak pulse
APS + GS (n = 41)	7 (17.07)	4 (9.76)	6 (14.63)	13 (31.71)	6 (14.63)	3 (7.31)
GS regimen (n = 56)	21 (37.50)	16 (28.57)	22 (39.29)	34 (60.71)	18 (32.14)	14 (25.00)
χ^2 value	4.810	5.120	7.005	7.974	3.897	5.068
P value	0.028	0.024	0.008	0.005	0.048	0.024

APS: *Astragalus* polysaccharide; GS: Gemcitabine plus tegafur gimeracil oteracil potassium capsule (S-1).

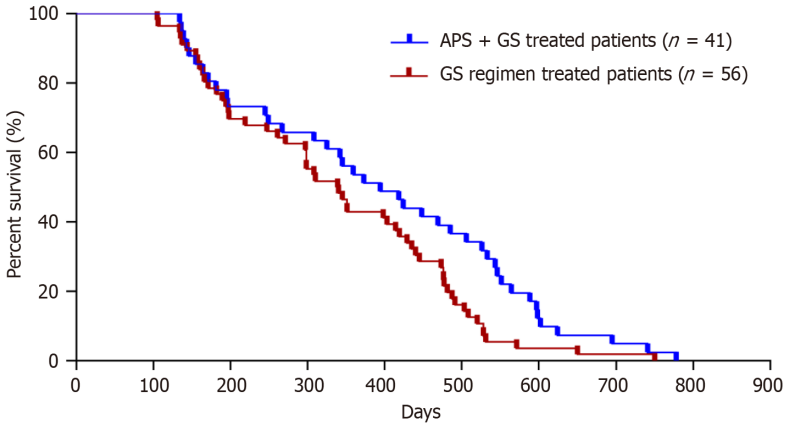

Figure 1 Survival curves. APS: *Astragalus* polysaccharide; GS: Gemcitabine plus tegafur gimeracil oteracil potassium capsule (S-1).

patients, impaired physiological function, lower drug tolerance, and chronic diseases may affect the implementation of chemotherapy. First-line chemotherapy effectiveness is an important factor affecting the long-term survival of patients with pancreatic cancer. In recent years, an increasing number of scholars have advocated comprehensive treatment for patients with pancreatic cancer, focusing on improving the efficacy of chemotherapy, prolonging survival time, and reducing chemotherapy-related adverse reactions.

APS is primarily sourced from *Astragalus*, which has the functions of tonifying Qi, consolidating the surface, strengthening the spleen, and benefiting the lungs and liver. This substance is commonly used for the conditioning of malignant tumors in TCM. In this study, patients receiving the combined therapy of APS and GS with pancreatic cancer achieved a significantly higher ORR and DCR (51.22% and 56.10%, respectively) compared with those receiving the monotherapy of GS alone (30.36%, 35.71%) after four cycles of chemotherapy (Table 2). Besides, the median OS time of patients receiving the combined therapy of APS and GS was longer than those receiving the monotherapy of GS alone (P < 0.05; Figure 1). APS also effectively improved fatigue, thick greasy tongue coating, and weak pulse in patients receiving the combined therapy of APS and GS (Table 4).

It has been confirmed in many *in vitro* and *in vivo* studies that APS can enhance immune activity, improve the local hematopoietic environment in the bone marrow, and accelerate stem cell proliferation, thereby inhibiting the occurrence and progression of tumors[19-21]. Duan and Wang[22] found that APS led to a significantly lower degree of myelosuppression after chemotherapy in patients with malignant tumors[22]. The results of a meta-analysis also showed that APS-based TCM decoction can increase the effectiveness and reduce the toxicity of platinum-based chemotherapy for advanced non-small cell lung cancer in randomized clinical trials[23]. In addition, APS alleviated the hepatic pathological damage in mice caused by epirubicin, cyclophosphamide, and docetaxel[24], which may be related to decreased cell senescence biomarkers, oxidative stress, and NOD-, LRR- and pyrin domain-containing protein 3-mediated pyroptosis and apoptosis *via* the adenosine monophosphate-activated protein kinase/mammalian target-of-rapamycin pathway[25]. Notably, APS treatment alleviated hepatotoxicity by down-regulating the expression of PTRF and co-localization of toll-like receptor 4 (TLR4)/PTRF, which contributed to alcohol-induced hepatic fibrosis[26]. For the immune system, APS was identified as a multiple immune activator, which can stimulate the maturation and antigen presentation of IL-12-producing dendritic cells (DCs) and then activate T cells[27] by interacting with anti-TLR4 on CD4+ CD25+ Treg cells. APS caused the transition from Th2 to Th1 CD4+T cells[28,29]. Additionally, APS can activate B cells through TLR4[30]. Similarly, APS could increase the secretion of immunomodulatory factors in macrophages *via* the MyD88-dependent signaling pathway mediated by TLR4[31,32]. Hwang *et al*[33] conducted a study on pulmonary metastatic melanoma in mice by combining APS treatment with immune checkpoint blockade. They found that the intranasal treatment of APS increased the number of lineage-CD11c+ DCs in the mesenteric lymph node (mLN) by up-regulating the expression of the CC-chemokine receptor 7. Further, intranasal treatment of APS activated DCs, which further stimulated natural killer and T cells in the mLN[33]. Moreover, APS treatment increased the frequency of $CD11c^{high}CD45RB^{low}$ DCs significantly

[34]. APS could up-regulate the expression of CD40, CD80, CD86, CD103, major histocompatibility complex I, and major histocompatibility complex II molecules[35,36] and multiply the generation of NO[37], thus inducing the maturation of DCs *in vivo*. Furthermore, it was demonstrated that APS promoted the proliferation of human peripheral blood mononuclear cells, augmented the secretion of cytokines in a time- and dose-dependent manner, and increased the secretion of IL-6[38]. It was also revealed that APS markedly activated peritoneal macrophages, increased TNF production, and induced the proliferation of LAK-like cytotoxic cells, thus resisting 12 rapidly proliferating tumor cell lines *in vitro*[39]. The toxic side effects of chemotherapy are important factors affecting its efficacy and compliance. Immune function suppression also occurs during chemotherapy, with T cells being an important cell subset mediating immune responses. In this study, it was demonstrated that patients receiving the combined therapy of APS and GS showed a lower incidence of leukopenia, thrombocytopenia, and liver function damage compared with those receiving the monotherapy of GS alone (Table 4). The percentages of CD3+ T cells and CD4+ T cells, the CD4+/CD8+ T cell ratio, and the serum IL-2 level were significantly ameliorated in patients receiving the combined therapy of APS and GS ($P < 0.05$). However, there was no significant difference in CD8+ T cells and serum INF-γ between these patients receiving the two therapies ($P > 0.05$; Table 3).

Based on the above studies, the data showed that APS could play an important role in promoting the proliferation of hematopoietic cells, strengthening the humoral and cellular immunity, and improving liver function effects during chemotherapy. In addition, APS could be applied as an adjuvant to enhance the host defense against primary and metastatic tumors and restore the depressed immune functions in the immune microenvironment.

Nevertheless, this study was limited by a small sample size and a retrospective analysis approach, which may introduce some subjectivity in case selection, thus requiring further validation in the future.

CONCLUSION

In conclusion, the combined therapy of APS and GS can improve short-term efficacy and long-term survival in the treatment of pancreatic cancer. Additionally, it can mitigate chemotherapy-induced immune suppression and toxic side effects, demonstrating positive clinical utility.

FOOTNOTES

Author contributions: Li GY contributed to data collection, analyzed the data, drafted the first draft; Jiang J conducted guidance and edited the manuscript; All authors have read and approved the final manuscript.

Institutional review board statement: This study was approved by the Ethics Committee of Zhejiang Provincial Hospital of Chinese Medicine (Ethics No. 2024-KLS-266-02).

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