

World Journal of *Clinical Cases*

World J Clin Cases 2020 July 6; 8(13): 2674-2892



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ABOUT COVER

Editorial board member of *World Journal of Clinical Cases*, Dr. El Ghoch is a Full Professor in the Faculty of Health Sciences, Beirut Arab University, Lebanon. Having received his MD degree from University of Bologna, Italy in 2005, and undertook his postgraduate degree in Clinical Nutrition at the University of Modena and Reggio Emilia, Italy in 2009. In the following 10 year, he had a wide clinical and research activity in Italy in the field of obesity and eating disorders, and gained an international leadership in the study of the body composition in anorexia nervosa. In October 2018 he was appointed as Professor in the Clinical Nutrition, and Chairperson of the Department of Nutrition and Dietetics, Beirut Arab University, Lebanon. His ongoing research interests are body composition, physical activity, weight cycling, etc.

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The *WJCC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, PubMed, and PubMed Central. The 2020 Edition of Journal Citation Reports® cites the 2019 impact factor for *WJCC* as 1.013 (5-year impact factor: N/A), ranking *WJCC* as 120 among 165 journals in medicine, general and internal (quartile in category Q3).

RESPONSIBLE EDITORS FOR THIS ISSUE

Electronic Editor: Yan-Xia Xing, Production Department Director: Yun-Xiaojian Wu, Editorial Office Director: Jin-Lai Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Semimonthly

EDITORS-IN-CHIEF

Dennis A Bloomfield, Sandro Vento, Bao-Gan Peng

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

July 6, 2020

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Retrospective Study

Adjuvant nab-paclitaxel plus gemcitabine vs gemcitabine alone for resected pancreatic ductal adenocarcinoma: A single center experience in China

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Supported by the China Postdoctoral Science Foundation, No. 2015M582853.

Institutional review board

statement: The study was approved by the Institutional Review Board of the Chinese People's Liberation Army General Hospital (S2016-098-02).

Informed consent statement:

Patients were not required to give informed consent to the study

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Abstract

BACKGROUND

Nab-paclitaxel plus gemcitabine (AG) has resulted in higher tumor response and survival rates for metastatic or advanced pancreatic ductal adenocarcinoma (PDAC) compared with gemcitabine (GEM) alone.

AIM

To examine the feasibility and safety of AG adjuvant chemotherapy of resectable PDAC.

METHODS

We retrospectively analyzed patients with resected PDAC who received AG or GEM as postoperative adjuvant treatment between January 2013 and December 2016 at the Chinese People's Liberation Army General Hospital, Beijing, China. The patients adopted combined nab-paclitaxel (125 mg/m²) and GEM (1 g/m²) or GEM (1 g/m²) alone treatment, on days 1 and 8 every 3 wk for six cycles, unless intolerable adverse events or disease progression occurred. The disease-free survival, overall survival (OS) and adverse events of the two groups were statistically analyzed.

RESULTS

Compared with GEM, median disease-free survival (12.2 mo *vs* 15.8 mo, *P* = 0.039) and OS (20.6 mo *vs* 28.3 mo, *P* = 0.028) were significantly improved in the AG group. The 2-year OS rates were 63.3% and 43.3% in the AG and GEM groups,

because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For full disclosure, the details of the study are published on the home page of Fukushima Medical University.

Conflict-of-interest statement: The authors declare that there is no conflict of interest related to this study.

Data sharing statement: Due to the sensitive nature of the questions asked in this study, survey respondents were assured raw data would remain confidential and would not be shared.

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Manuscript source: Unsolicited manuscript

Received: March 15, 2020

Peer-review started: March 15, 2020

First decision: April 22, 2020

Revised: May 2, 2020

Accepted: June 7, 2020

Article in press: June 7, 2020

Published online: July 6, 2020

P-Reviewer: Aktekin A, Karamouzian MV

S-Editor: Dou Y

L-Editor: Filipodia

E-Editor: Xing YX



respectively. However, the incidence of sensory neuropathy was increased significantly in the AG than the GEM group (53.3% *vs* 23.3%, $P < 0.001$).

CONCLUSION

In our initial experience, AG significantly improved disease-free survival and OS of patients with resected PDAC. AG may be a potential option for postoperative adjuvant chemotherapy of resectable PDAC.

Key words: Nab-paclitaxel; Gemcitabine; Pancreatic ductal adenocarcinoma; Surgery; Adjuvant; Resectable

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Core tip: Nab-paclitaxel plus gemcitabine (AG) has resulted in better survival and tumor response rates for advanced or metastatic pancreatic ductal adenocarcinoma (PDAC) compared with gemcitabine alone. However, its role in adjuvant therapy for resected PDAC remains unclear. We retrospectively reviewed our PDAC database for patients with primary resectable PDAC who were treated with AG or gemcitabine alone as postoperative adjuvant chemotherapy between January 2013 and December 2016. Our results suggested that AG significantly improved disease-free survival and overall survival of patients with resected PDAC. AG may be a potential option for postoperative adjuvant chemotherapy of resectable PDAC.

Citation: Yin ZZ, Zhao ZM, Tang WB, Jiang N, Zhang KD, Song YY, Wang Y, Li CG, Gao YX, Liu R. Adjuvant nab-paclitaxel plus gemcitabine *vs* gemcitabine alone for resected pancreatic ductal adenocarcinoma: A single center experience in China. *World J Clin Cases* 2020; 8(13): 2778-2786

URL: <https://www.wjgnet.com/2307-8960/full/v8/i13/2778.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v8.i13.2778>

INTRODUCTION

The mortality rate of patients with pancreatic ductal adenocarcinoma (PDAC) is increasing. In China, PDAC is the sixth leading cause of cancer-related death^[1]. Complete resection of the involved portion of the pancreas has shown a curative effect. Although improved surgical techniques have led to more patients undergoing radical resection, the 5-year survival rate after radical resection alone is $< 10\%$ ^[2,3]. Therefore, postoperative adjuvant treatments have been evaluated over the past several decades.

The ESPAC-1^[4] and CONKO-001^[5] trials showed that postoperative adjuvant systemic chemotherapy [fluorouracil or gemcitabine (GEM)] improves survival of patients with resected PDAC. The ESPAC-4 trial^[6], published in 2017, demonstrated the superiority of combination of GEM and capecitabine in the adjuvant setting (median survival 26 mo, 5-year survival rate approximately 30%). Surgery followed by adjuvant GEM monotherapy or GEM plus capecitabine is the standard of care for potentially curable pancreatic cancer. Additionally, the JASPAC 01 trial^[7] showed that adjuvant chemotherapy with S-1 can be effective for resected pancreatic cancer in Japanese patients. However, recurrence rates remain high despite microscopically and pathologically complete removal of the tumor and adjuvant chemotherapy with about 69%–75% of patients experiencing recrudescence within 2 years^[8–10].

Nab-paclitaxel combination with GEM (AG) significantly improves disease-free survival (DFS), overall survival (OS) and tumor response rates of patients with metastatic or local advanced pancreatic adenocarcinoma^[11–13]. Therefore, we explored the efficacy and safety of AG compared with GEM alone as adjuvant therapy for patients with resected PDAC.

MATERIALS AND METHODS

Patients

We retrospectively reviewed our PDAC database for patients with primary resectable PDAC who were treated with AG or GEM alone as postoperative adjuvant chemotherapy between January 2013 and December 2016. The study was approved by the Ethics Committee of the Chinese People's Liberation Army General Hospital (No. S2016-098-02). Patients aged 18–79 years were recruited and had received complete macroscopic resection (R0 or R1)^[14] for histologically confirmed PDAC. The other inclusion criteria were full recovery from surgery (3–12 wk after the operation), Eastern Cooperative Oncology performance status of 0 or 1 and adequate hematological, liver and renal function according to measurements^[15] performed 7 d before initiation of adjuvant therapy. Patients with incomplete (R2) resection, nonductal adenocarcinoma, TNM stage IV disease^[16] or serious complications (Clavien–Dindo grade III or above) were excluded. Additionally, patients were excluded if they had recurrence or metastatic disease on chest radiography and contrast-enhanced abdominal computed tomography or magnetic resonance imaging before initiation of adjuvant therapy. Postoperative carbohydrate antigen 19-9 level was not restricted.

Treatment regimens

Patients were assigned to receive the AG regimen or GEM alone. GEM was delivered as a 1 g/m² intravenous infusion, and AG regimen consisted of 125 mg/m² nab-paclitaxel (Abraxane) followed by 1 g/m² GEM. Both regimens were administered on days 1 and 8 every 3 wk (one cycle) for 24 wk (six cycles). During each cycle or whenever clinically indicated, patient status was assessed *via* a comprehensive physical examination, World Health Organization performance status assessment, whole blood cell count and blood biochemical examination. Follow-up evaluation included contrast-enhanced computed tomography or magnetic resonance imaging of the chest, abdomen and pelvis and measurement of tumor markers. Clinical examinations were repeated at 3-mo intervals for 2 years and subsequently at 6-mo intervals for 3 years.

Chemotherapy-related toxicity

Chemotherapy-related toxicity was evaluated and graded by the National Cancer Institute Common Terminology Criteria of Adverse Events, version 4.0^[17]. The grade 3 or higher was defined as the severe adverse events. Safety evaluations were carried out before each cycle and until the end of follow-up.

Adjuvant treatment was continued until intolerable adverse events or disease progression occurred. Details of dose modifications, adverse events and treatment cessation are reported elsewhere^[8,18]. In the AG group, nab-paclitaxel was adjusted at a dose of 60 mg/m² for the patients of grade 2 neutropenia or grade 1 thrombocytopenia. Adjuvant chemotherapy was postponed for a maximum of 2 wk for patients of grade 3 or 4 neutropenia, anemia or thrombocytopenia. If the treatment was delayed because of febrile neutropenia, then granulocyte colony-stimulating factor was used in subsequent cycles.

Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics, version 20.0 (IBM Corp., Armonk, NY, United States). The continuous variables of normal distribution were expressed as mean $\pm$ standard deviation and those of abnormal distribution as median with minimum to maximum values. Differences in continuous variables between two groups were compared by *t* test or Mann–Whitney test, according to the distribution of the data. The frequencies of categorical variables were examined by χ^2 test. If the observed number in one or more cells was > 1 but < 5 , or the table was more than 2×2 , then likelihood ratio statistics were calculated. If at least one expected cell count was < 1 in a 2×2 table, then Fisher's exact test was performed. Two-tailed statistical analyses were conducted. A Kaplan–Meier algorithm was used to compare survival. Differences were considered significant at $P < 0.05$.

RESULTS

From January 2013 to December 2016, 70 patients with PDAC were assigned to receive an adjuvant regimen, of whom, ten were excluded due to serious complications or R2

resection. As a result, 30 patients each were assigned to the AG and GEM groups. Both groups had similar demographic and clinical characteristics at baseline (Table 1).

At the last follow-up on January 20, 2019, the median follow-up duration was 22 mo in the GEM group and 27 mo in the AG group. Patients alive and without disease progression at the time of the final analysis were censored at the date of last follow-up. The median OS was 20.6 mo [95% confidence interval (CI): 11.2-29.9 mo] in the GEM group and 28.3 mo (95%CI: 21.9-34.6 mo) in the AG group ($P = 0.028$). The median DFS was 12.2 mo (95%CI: 9.6-14.8 mo) in the GEM group and 15.8 mo (95%CI: 13.1-18.5 mo) in the AG group ($P = 0.039$) (Figure 1). Recurrence was observed in 27 of 30 (90%) patients in the GEM group and in 24 of 30 (80%) patients in the AG group. Seven patients (23.3%) in the GEM group and eleven (36.7%) in the AG group were alive at the end of the analysis. The 2-year OS rates were 63.3% and 43.3% in the AG and GEM groups, respectively.

There were 15 patients (50%) in the AG group and 17 patients (56.7%) in the GEM group who received all planned cycles of chemotherapy. The median chemotherapy cycles were 5.5 (range 1-6) in the AG group and six (range 2-6) in the GEM group ($P = 0.402$). All patients were in the safety set and were analyzed for adverse events.

In the GEM group, 13 (43.3%) patients had 81 adverse events. In the AG group, 18 patients (60%) had 143 adverse events (Table 2). The incidence of decreased white blood cell count, neutropenia, anemia, thrombocytopenia, fatigue, vomiting, diarrhea, fever, febrile neutropenia and infection were similar in both groups. However, the incidence of sensory neuropathy was significantly increased in the AG group than the GEM group (53.3% *vs* 23.3%, $P < 0.001$). Additionally, grade 3 or higher neutropenia was more common in the AG group than GEM group (43.3% *vs* 30%), but the frequency of granulocyte colony-stimulating factor use did not differ significantly between the two groups (41.9% in the AG group *vs* 24.1% in the GEM group, $P = 0.177$).

DISCUSSION

In this retrospective study involving patients with resected PDAC, adjuvant chemotherapy with AG significantly increased OS and DFS compared with GEM alone. The safety and toxicity profiles of AG were acceptable and manageable, as in previous trials of advanced metastatic pancreatic adenocarcinoma.

The median OS and DFS in the GEM group were 20.1-26.5 and 11.3-15.3 mo, respectively, which was similar to previous studies^[6-8,10]. However, the median OS was 7.7 mo longer in the AG group than in the GEM group (28.3 mo *vs* 20.6 mo, $P = 0.028$). The median DFS was 15.8 mo in the AG group and 12.2 mo in the GEM group ($P = 0.039$). Treatment with AG led to a 20% improvement in the 2-year OS rate (63.3% in the AG group *vs* 43.3% in the GEM group).

Nab-paclitaxel possesses antitumor activity and acts synergistically with GEM. Nab-paclitaxel also improves the intratumoral concentration of GEM^[19]. The efficacy and safety of AG as first-line treatment for borderline resectable and locally advanced and metastatic pancreatic cancer have been reported^[11,13,18,20-21]. Although this was a single-center retrospective study, the outstanding OS observed suggests the efficacy of the AG combination, which warrants further investigation for resectable PDAC.

As expected, the rates of serious life-threatening adverse events in the AG and GEM groups were similar and acceptable. Compared with the GEM group, the grade 3 or higher neutropenia was more frequent in the AG group (30% *vs* 43.3%), but there was no significant difference in the frequency of granulocyte colony-stimulating factor use ($P = 0.177$), febrile neutropenia ($P = 0.073$) or infection ($P = 0.550$). However, the incidence of sensory neuropathy differed significantly between the AG and GEM groups (53.3% *vs* 23.3%, $P < 0.001$). If grade 3 or higher sensory neuropathy was diagnosed, then the dose of nab-paclitaxel was subsequently reduced or temporarily discontinued.

Conroy *et al*^[22] reported that adjuvant chemotherapy with a modified FOLFIRINOX (combination of fluorouracil, oxaliplatin, irinotecan and leucovorin) treatment led to significantly longer survival than GEM did among patients with resected PDAC (DFS, 21.6 mo *vs* 12.8 mo; OS, 54.4 mo *vs* 35 mo). However, there was a significant increase in the incidence of adverse effects. Therefore, the modified FOLFIRINOX regimen is not frequently applied in China, especially in the adjuvant setting for resected PDAC^[23].

Results of the global phase III APACT trial have been reported at ASCO 2019. The APACT trial revealed that there was no statistical benefit for adjuvant chemotherapy with AG by independent central review^[24,25]. The median DFS by independent review

Table 1 Demographic and clinical characteristics of the patients at baseline, *n* (%)

Characteristic	AG	GEM	<i>P</i> value
Age in yr	57 (40-72)	59 (31-67)	
Sex			0.787
Male	19 (63)	20 (67)	
Female	11 (37)	10 (33)	
Performance status			0.791
0	19 (63.3)	18 (60)	
1	11 (36.7)	12 (40)	
Diabetes			0.559
No	23 (77)	21 (70)	
Yes	7 (23)	9 (30)	
Operative procedure			0.605
Pancreatoduodenectomy	15 (50)	17 (57)	
Distal pancreatectomy	15 (50)	13 (43)	
Residual tumor status			0.687
R0	27 (90)	26 (87)	
R1	3 (10)	4 (13)	
Primary tumor status			0.638
T1	6 (20.0)	3 (10.0)	
T2	17 (56.7)	20 (66.7)	
T3	5 (16.6)	6 (20.0)	
T4	2 (6.7)	1 (3.3)	
Regional lymph node status			0.273
N0	22 (73)	18 (60)	
N1	8 (27)	12 (40)	
Pathological stage			0.405
I (IA/IB)	17 (5/12, 56.7)	13 (1/12, 43.4)	
II (IIA/IIB)	11 (4/7, 36.6)	16 (5/11, 53.3)	
III	2 (6.7)	1 (3.3)	
Tumor grade			0.105
Well differentiated	3 (10)	2 (6.7)	
Moderately differentiated	23 (76.7)	17 (56.7)	
Poorly differentiated	4 (13.3)	11 (36.6)	
Pre-adjuvant CA19-9, median	48.2	24.6	0.795
≤ 37 U/mL	13 (43.4)	14 (46.7)	
> 37 U/mL	17 (56.6)	16 (53.3)	

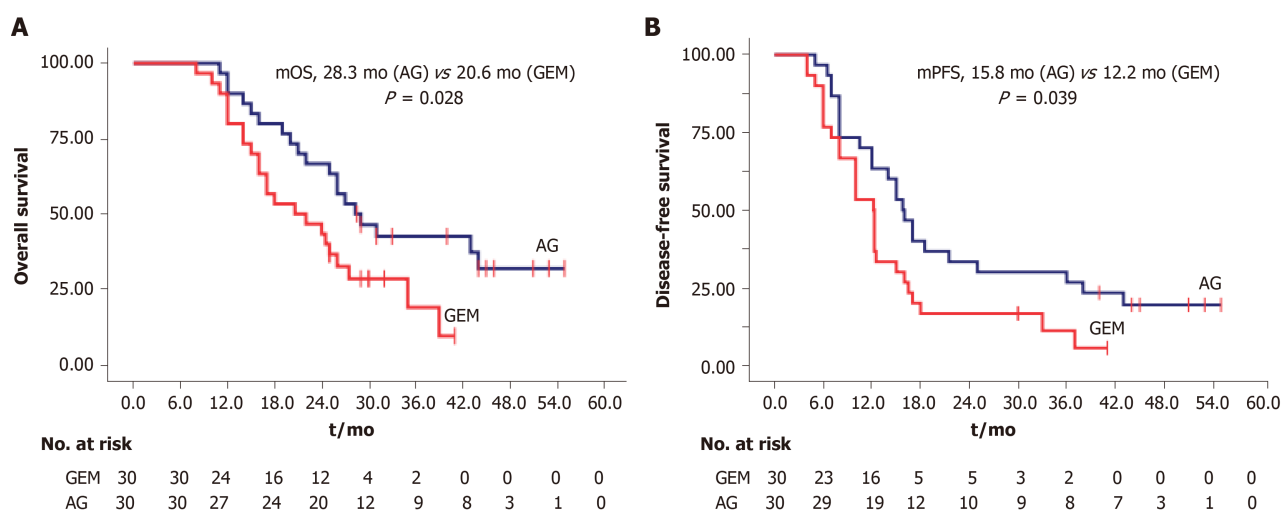
AG: Nab-paclitaxel plus gemcitabine; GEM: Gemcitabine.

was 19.4 mo in the AG group and 18.8 mo in the GEM group ($P = 0.1824$). However, the sensitivity analysis of investigator assessment demonstrated a significant improvement for both DFS (16.6 mo *vs* 13.7 mo, $P = 0.0168$) and OS (40.5 mo *vs* 36.2 mo, $P = 0.045$) with the use of AG as compared to GEM only. The ongoing Phase III APACT study is investigating survival for adjuvant GEM compared with AG for resected PDAC. We look forward to seeing the results of this study that are expected

Table 2 Adverse events with nab-paclitaxel plus gemcitabine and gemcitabine alone

	AG			GEM			<i>P</i> value	<i>P</i> value Grade $\geq$ 3
	Grade 1/2 (%)	Grade 3/4 (%)	Grade 5 (%)	Grade 1/2 (%)	Grade 3/4 (%)	Grade 5 (%)		
White blood cell count decreased	8 (26.7)	9 (30.0)	0	7 (23.3)	6 (20.0)	0	0.549	0.371
Neutropenia	5 (16.7)	13 (43.3)	0	4 (13.3)	9 (30.0)	0	0.435	0.284
Anemia	10 (33.3)	3 (10.0)	0	6 (20.0)	3 (10.0)	0	0.489	1.000
Thrombocytopenia	5 (16.7)	3 (10.0)	0	2 (6.7)	2 (6.7)	0	0.394	0.639
Fatigue	9 (30.0)	4 (13.3)	0	6 (20.0)	2 (6.7)	0	0.382	0.385
Vomiting	10 (33.3)	3 (10.0)	1 (3.3)	8 (26.7)	0	1 (3.3)	0.168	0.148
Diarrhea	8 (26.7)	1 (3.3)	0	6 (20.0)	0	0	0.392	1.000
Fever	8 (26.7)	2 (6.7)	0	5 (16.7)	1 (3.3)	0	0.496	0.550
Febrile neutropenia	2 (6.7)	4 (13.3)	1 (3.3)	3 (10.0)	1 (3.3)	0	0.296	0.073
Infection	2 (6.7)	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	0	0.615	0.550
Sensory neuropathy	14 (46.7)	15 (50.0)	1 (3.3)	7 (23.3)	0	0	< 0.001	< 0.001

AG: Nab-paclitaxel plus gemcitabine; GEM: Gemcitabine.

**Figure 1** Kaplan–Meier analysis of overall survival and disease-free survival according to treatment group. A: Kaplan–Meier analysis of overall survival according to treatment group; B: Kaplan–Meier analysis of disease-free survival according to treatment group. AG: Nab-paclitaxel plus gemcitabine; GEM: Gemcitabine.

by 2022.

The present study had several limitations due to its retrospective study design. It was also a single-center, nonrandomized controlled study with potential selection bias. However, our results initially indicated the efficacy and safety of AG for resectable PDAC. In conclusion, AG may be a potential option for postoperative adjuvant chemotherapy of resectable PDAC.

ARTICLE HIGHLIGHTS

Research background

Nab-paclitaxel plus gemcitabine (AG) has resulted in better tumor response and survival rates for metastatic or advanced pancreatic ductal adenocarcinoma (PDAC)

compared with gemcitabine (GEM) alone. However, its role in adjuvant therapy for resected PDAC remains unclear.

Research motivation

This study aimed to examine the effects of AG and GEM alone as adjuvant therapy for resected PDAC.

Research objectives

This study examined the safety and efficacy of AG adjuvant therapy for resected PDAC.

Research methods

We retrospectively reviewed our PDAC database for patients with primary resectable PDAC who were treated with AG or GEM alone as postoperative adjuvant chemotherapy between January 2013 and December 2016.

Research results

The median follow-up duration was 22 mo in the GEM group and 27 mo in the AG group. Compared with GEM, median disease-free survival (12.2 mo *vs* 15.8 mo, $P = 0.039$) and overall survival (20.6 mo *vs* 28.3 mo, $P = 0.028$) were significantly improved in the AG group. The 2-year overall survival rates were 63.3% and 43.3% in the AG and GEM groups, respectively. However, the incidence of sensory neuropathy was significantly higher in the AG than in the GEM group (53.3% *vs* 23.3%, $P < 0.001$).

Research conclusions

This study suggested that AG significantly improved disease-free survival and overall survival of patients with resected PDAC. AG may be a potential option for postoperative adjuvant chemotherapy of resectable PDAC.

Research perspectives

The present study had several limitations due to its retrospective study design. It was also a single-center, nonrandomized controlled study with potential selection bias. However, our results initially indicated the efficacy and safety of AG for resectable PDAC. The ongoing Phase III APACT study is investigating survival for adjuvant GEM compared with AG for resected PDAC. We look forward to seeing the results of this study that are expected by 2022.

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