BMC Pharmacology and Toxicology

RESEARCH

Open Access

Risk comparison of adverse reactions between gemcitabine monotherapy and gemcitabine combined with albumin-bound paclitaxel in pancreatic cancer: insights from the FDA Adverse Event Reporting System (FAERS) database

Puen Jiang[1], Kezhen Zong[1], Dadi Peng[1], Baoyong Zhou[1] and Zhongjun Wu[1*]

Abstract

Background Pancreatic cancer (PC) is a highly aggressive malignancy with limited treatment options. Although gemcitabine monotherapy (G treatment) has long been a standard treatment, combination therapies, such as gemcitabine with albumin-bound paclitaxel (AG treatment), have shown improved outcomes and were approved by the FDA for the PC. However, the AG treatment is also associated with increased adverse events (AEs), which remain inadequately evaluated in real-world settings.

Methods We utilized the FDA Adverse Event Reporting System (FAERS) to conduct a large-scale pharmacovigilance analysis comparing the safety profiles of G and AG treatments for PC. By analyzing adverse event data from the third quarter of 2013 to the second quarter of 2024 and quantifying AE signals with reporting odds ratio (ROR) and proportional reporting ratio (PRR) methods, we compared the risk of AEs between the groups. Time to onset (TTO), subgroup and logistic regression analyses were also performed.

Results The study revealed a higher proportion of male ($n = 2307$, 54.1%) and elderly patients (age ≥ 65years, $n = 2172$, 50.9%) in the AG treatment group compared to the G treatment group. We found 17 preferred terms with positive signals at the top 50 common AEs, especially in gastrointestinal and blood systems. Cardiac and neurological AEs also needed to be vigilant. Biliary sepsis and infectious enterocolitis were newly identified AEs and deserve attention. Median TTO was 34 (IQR: 8-103) days (G) and 41 (IQR: 10–104) days (AG), with most AEs occurring within the first month (48.3% and 44%). Subgroup analysis revealed that male patients using the AG treatment had the highest risk of immune-mediated hepatitis (ROR = 23.51, 95% CI = 3.21–172.1), while elderly patients had elevated risks for presyncope (ROR = 24.84, 95% CI = 3.40–181.28) and falls (ROR = 18.60, 95% CI = 2.53–136.97). Logistic regression

*Correspondence:
Zhongjun Wu
wzjtcy@126.com

Full list of author information is available at the end of the article

showed higher-risk fatal outcomes in males (adjusted OR = 1.42, 95% CI = 1.15–1.76, $P < 0.01$) and elderly patients (adjusted OR = 1.36, 95% CI = 1.10–1.69, $P < 0.01$).

Conclusion This research offers critical safety insights in real-world settings, emphasizing patients at heightened AEs risk and informing clinical decision-making in PC treatment.

Keywords Pancreatic cancer, Gemcitabine, Albumin-bound paclitaxel, FAERS, Adverse event, Disproportionality analysis

Introduction

Pancreatic cancer (PC) is a highly aggressive malignancy, with a five-year survival rate of less than 12%, and is marked by rising incidence and mortality rates worldwide [1]. Despite advancements in cancer treatment, therapeutic options for PC remain limited, and progress in improving patient outcomes has been slow [2]. Therefore, developing effective and safe treatment regimens is crucial for enhancing patients' survival and quality of life with PC.

Since its approval in 1997, gemcitabine has been a cornerstone of first-line treatment for advanced PC [3]. However, gemcitabine's effectiveness as a standalone treatment is limited. To improve treatment outcomes, researchers have explored various combination therapies [4–6]. Among these, the combination of gemcitabine and albumin-bound paclitaxel (the AG treatment) was approved by the Food and Drug Administration (FDA) in 2013 for the treatment of metastatic PC, representing a significant breakthrough [6]. This combination therapy demonstrated substantial survival benefits in a phase III clinical trial, extending the median overall survival from 6.7 months with gemcitabine alone to 8.5 months [7]. Although the advantages of the AG treatment in terms of efficacy, safety concerns cannot be overlooked. Compared to gemcitabine monotherapy (G treatment), the AG treatment may increase the incidence and severity of certain adverse reactions. In previous clinical trials, the major adverse reactions associated with AG treatment included myelosuppression, peripheral neuropathy, and fatigue [7]. However, existing studies primarily focus on efficacy, with safety assessments limited to small sample sizes. Moreover, due to the strict eligibility criteria and controlled environments, safety data from clinical trials may not fully reflect real-world settings. Currently, there is a lack of large-scale post-marketing safety studies on the use of AG for treating PC.

The FDA Adverse Event Reporting System (FAERS) is a spontaneous reporting database that offers advantages such as large sample sizes, broad coverage, and reflection of real-world medication usage [8]. Utilizing this database enables large-scale pharmacovigilance analyses to compare the safety profiles of different treatment regimens. Therefore, this study aims to utilize the FAERS database to compare the risk of adverse events (AEs) associated with G and AG treatments in patients with PC, exploring the time to onset of AEs and potential risk factors influencing patients' fatal outcomes. This research hopes to provide comprehensive safety reference information for clinical practice, including treatment selection and the prevention and management of AEs.

Methods

Data extraction and processing

The study workflow is presented in Fig. 1a. Data were sourced from the FAERS database, containing adverse event reports (AERs) submitted to the US FDA by healthcare professionals, consumers, and manufacturers [9]. The data extraction period covered the third quarter of 2013 to the second quarter of 2024 and included seven sections: patient demographic (DEMO), drug-related information (DRUG), adverse event data (REAC), reported source information (RPSR), therapeutic start and end dates of the reported drugs (THER), drug usage or diagnostic indications (INDI), and patient outcomes related to adverse events (OUTC) [10]. Specifically, DEMO provided patient details like age, gender, weight and country; REAC supplied adverse event data; DRUG included drug names and therapeutic specifics; RPSR provided the reporter's profession; OUTC covered patient outcomes; THER offered therapeutic start/end dates and adverse event onset times; and INDI provided diagnostic and drug usage information.

Duplicate records were removed according to the recommended methodology. The fields PRIMARYID, CASEID, and FDA_DT (the submission date of the report to the FDA) from the DEMO file were selected. For cases with duplicate CASEIDs, the record with the most recent FDA_DT or the highest PRIMARYID was retained. As shown in Fig. 1b, adverse events in the REAC file were standardized using the Medical Dictionary for Regulatory Activities (MedDRA, version 27.0) [11]. MedDRA is a hierarchical terminology system composed of multiple levels, starting from the most specific Lower Level Term (LLT) to Preferred Term (PT), High Level Term (HLT), High Level Group Term (HLGT), and finally, System Organ Class (SOC). The standardization process mapped the originally reported adverse event terms to the corresponding standardized MedDRA terms. This study primarily focused on the SOC and PT levels. Regarding

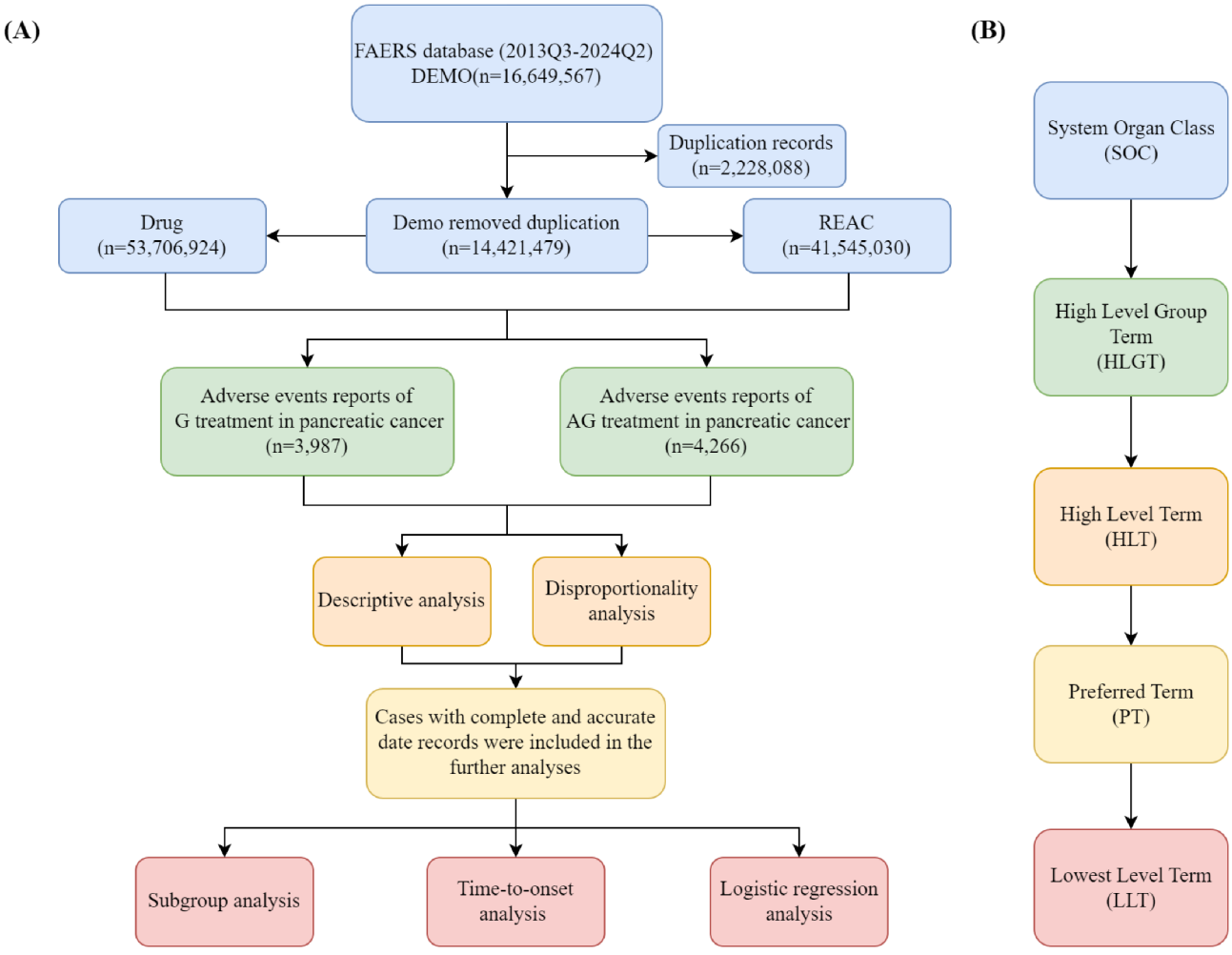

Fig. 1 The flow chart of this study. Abbreviations: G treatment, gemcitabine monotherapy; AG treatment, gemcitabine combined with albumin-bound paclitaxel

the OUTC file, adverse event outcomes were categorized according to the FAERS database's definition, such as death, hospitalization, or life-threatening conditions. Notably, the term "Other Serious" is also a predefined category that meets the FDA's criteria for seriousness but does not fall into the specific predefined categories.

The keywords "gemcitabine" and "albumin-bound paclitaxel" were used to retrieve relevant drug records from DRUG file. The inclusion criteria for drugs were as follows: 1. G treatment group: Drug A (gemcitabine) was the primary suspect (PS) for suspected drugs, whereas drug B (albumin-bound paclitaxel) was excluded (as a secondary suspect drug, SS; concomitant drug, C; or interacting drug, I). 2. AG treatment group: cases containing drug A (PS) plus drug B (SS, C, I) or drug B (PS) plus drug A (SS, C, I). To identify AERs related to pancreatic cancer, INDI file was searched using the following terms: "pancreatic carcinoma", "adenocarcinoma pancreas", "ductal adenocarcinoma of pancreas", "cystadenocarcinoma pancreas", "acinar cell carcinoma of pancreas", "pancreatic carcinoma metastatic", "pancreatic carcinoma recurrent", "pancreatic carcinoma stage iii", "pancreatic carcinoma stage iv".

Disproportionality analysis

Disproportionality analysis is a widely used signal detection technique in pharmacovigilance, aimed to identify potential drug safety signals by analyzing the reporting ratios of drugs and adverse drug reactions (ADRs) in the FAERS database. In this study, we utilized the reporting odds ratio (ROR) and proportional reporting ratio (PRR) methods, based on the 2×2 contingency table (Table 1), to identify and compare the associations between drugs and ADRs [12, 13]. Both methods showed high sensitivity and strong performance in early signal detection [14]. The criteria for signal detection were as follows: ROR, lower limit of the 95% CI (ROR025) > 1, case reports ≥ 3 and PRR ≥ 2, chi-squared value (χ^2) ≥ 4. The relevant formulas are provided in Supplementary Table 1. The association was identified as a potential safety signal when

Table 1 Two-by-two contingency table for disproportionality analysis

Drug	Target AEs	Other AEs	Total
Gemcitabine combined with albumin-bound paclitaxel	a	b	a + b
Gemcitabine	c	d	c + d
Total	a + c	b + d	a + b + c + d

Abbreviation AEs, adverse events; a, number of reports containing both the gemcitabine combined with albumin-bound paclitaxel and target adverse drug reaction; b, number of reports containing other adverse drug reaction of the gemcitabine combined with albumin-bound paclitaxel; c, number of reports containing the target adverse drug reaction of gemcitabine; d, number of reports containing other adverse drug reactions of gemcitabine

the results met the threshold criteria for both methods, indicating that the risk of AE was higher with AG treatment compared to G treatment. The European Medicines Agency (EMA) establishes important medical events (IMEs), including AEs characterized by severity. Subgroup analyses were conducted by age (18–64 years and ≥ 65 years) and gender (male and female) to explore potential risk differences in ADRs among different populations. Furthermore, a risk comparison of AEs was also made between the two treatment groups within the first 30 days of onset.

Time-to-onset (TTO) analysis

Time to onset (TTO) was defined as the interval between the date of the AE (EVENT_DT) and the start date of the drug administration (START_DT). Only cases with complete and accurate date records were included in the analysis. TTO was stratified, and the median and interquartile range (IQR) were used to quantitatively describe the distribution of adverse event occurrence. TTO was compared between groups using the Mann-Whitney U test. Subsequently, the Weibull shape parameter (WSP) was performed to model changes in AE incidence over time for the two treatment groups [15]. The WSP parameter β was used to evaluate the failure type of the AE: when $\beta = 1$, it indicates random AE occurrence; when $\beta < 1$, the risk of AE decreases over time; and when $\beta > 1$, the risk of AE increases over time.

Logistic regression analysis

To investigate factors associated with fatal outcomes (Death), accounting for 17% of cases in the G treatment and 16% in the AG treatment. We performed univariable and multivariable logistic regression analyses. The independent variables included age, gender, weight, and drug treatment group (G and AG treatment). Age was categorized into two groups: <65 years and ≥ 65 years, while weight was divided into three categories: <80 kg, 80–100 kg, and >100 kg. P-values less than 0.05 were considered statistically significant.

Table 2 Clinical characteristics of patients with pancreatic cancer in two treatment groups from the FAERS database

Characteristics (*n* = 8253)	Gemcitabine	Gemcitabine combined with albumin-bound paclitaxel
Number of reports, ***n***(%)	3987 (48.3)	4266 (51.7)
Gender, ***n***(%)		
Male	1474 (37.0)	2307 (54.1)
Female	1129 (28.3)	1722 (40.4)
Missing	1384 (34.7)	237 (5.6)
Age (years), ***n***(%)		
Median (IQR)	66 (59–73)	67 (59–72)
< 18	11 (0.2)	6 (0.1)
18–64	1084 (27.2)	1531 (35.9)
≥ 65	1398 (35.1)	2172 (50.9)
Missing	1494 (37.5)	557 (13.1)
Weight (kg), ***n***(%)		
Median (IQR)	65 (56.8–78)	68 (58–79)
< 50	66 (1.7)	209 (4.9)
50–100	671 (16.8)	1666 (39.1)
> 100	36 (0.9)	85 (2.0)
Missing	3214 (80.6)	2306 (54.1)
Reporter, ***n***(%)		
Consumer	582 (14.6)	376 (8.8)
Health Professional	685 (17.2)	542 (12.7)
Physician	1103 (27.7)	1740 (40.8)
Other Professional	1406 (35.3)	1395 (32.7)
Pharmacist	162 (4.1)	202 (4.7)
Missing	49 (1.2)	11 (0.3)

Abbreviation interquartile range, IQR

R Software (Version 4.2.1) and Microsoft Excel (Version 2021) were used for all analyse.

Results

Descriptive analysis

In Table 2, 3987 (48.3%) reports of pancreatic cancer patients received gemcitabine monotherapy, while 4266 (51.7%) received gemcitabine combined with albumin-bound paclitaxel, based on the total number of reports ($n = 8253$). The AG treatment group had a higher proportion of male patients (54.1% vs. 37.0%) and older patients (median age: 67 years, IQR 59–72, with 50.9% aged ≥ 65 years) compared to the G treatment group (median age: 66 years, IQR 59–73, with 35.1% aged ≥ 65 years). Regarding weight, a greater proportion of patients in the AG treatment group weighed between 50 and 100 kg (39.1% vs. 16.8% in the G treatment group), although missing data were considerable in both groups (54.1% and 80.6%, respectively). In terms of reporting sources, physicians contributed more reports in the AG treatment group (40.8% vs. 27.7% in the G treatment group), with additional reports from other professionals and consumers.

Figure 2a illustrates the number of reported cases between 2013 and 2024. During the early years (2013–2015), the number of G treatment-reported cases increased steadily, reaching a peak of 521 in 2015. In contrast, the AG treatment initially had very few reports (27 in 2013), but this number surged to 606 by 2016, with a subsequent peak of 639 in 2020. Figure 2b and c present that the top reporting countries for G treatment include the United States (1369 reports; 34.3%), followed by Japan (611 reports; 15.3%) and France (358 reports; 9.0%). For AG treatment, the United States again ranks first (868 reports; 20.3%), closely followed by Canada (818 reports; 19.2%) and Japan (479 reports; 11.2%). The largest proportion of outcomes reported for G treatment was categorized as "Other Serious," accounting for 54% of the total cases. Hospitalization and death were also important outcomes, comprising 23% and 17% of the cases, respectively (Fig. 2d). For AG treatment, hospitalization was the most frequent outcome (44% of cases), followed by "Other Serious" (33%) and death (16%) (Fig. 2e).

Figure 3 displays the number of AEs categorized by SOC for the two treatment groups. The G treatment group reported 10,540 adverse reactions, while the AG treatment group reported 12,041. For G treatment, the top three SOC categories were general disorders and administration site conditions (1861 cases), blood and lymphatic system disorders (1738 cases), and gastrointestinal disorders (1163 cases). The top three SOC categories for AG treatment were gastrointestinal disorders (1746 cases), blood and lymphatic system disorders (1687 cases), and general disorders and administration site conditions (1556 cases).

Comparison of safety signals between AG and G treatments at the PT level using disproportionality analysis

According to the ranking of the top 50 frequency of PTs in the AG treatment group, a total of 17 positive safety signals (PTs) were identified, of which 9 were classified as IMEs, which indicates that the risk of these AEs is higher with AG treatment than with G treatment (Table 3). In the comparison of AG treatment to G treatment, notable signals in the blood and lymphatic system disorders included febrile neutropenia (ROR = 2.47, 95% CI = 1.86–3.29), and disseminated intravascular coagulation (ROR = 2.15, 95% CI = 1.28–3.62). Gastrointestinal disorders also demonstrated significant positive signals, including abdominal pain (ROR = 2.24, 95% CI = 1.72–2.93), constipation (ROR = 2.91, 95% CI = 1.87–4.51), upper gastrointestinal haemorrhage (ROR = 4.49, 95%CI = 2.2–9.17), colitis (ROR = 2.23, 95% CI = 1.36–3.66), and stomatitis (ROR = 3.88, 95% CI = 2.07–7.26). Infections and infestations were highlighted with signals for sepsis (ROR = 2.79, 95% CI = 2.14–3.65), pneumonia (ROR = 2.39, 95% CI = 1.78–3.2), biliary tract infection (ROR = 20.24, 95% CI = 6.37–64.33), and infection (ROR = 2.15, 95% CI = 1.28–3.62). Nervous system disorders included cerebrovascular accident (ROR = 3.18, 95% CI = 1.83–5.54) and paraesthesia (ROR = 7.17, 95% CI = 3.07–16.75). Investigations revealed neutrophil count decreased (ROR = 2.39, 95% CI = 1.59–3.59). Additionally, metabolism and nutrition disorders included dehydration (ROR = 2.23, 95% CI = 1.58–3.15), and vascular disorders noted hypotension (ROR = 3.51, 95% CI = 2.03–6.08). Cardiac disorders, such as atrial fibrillation (ROR = 2.87, 95% CI = 1.61–5.11), were also observed. All PTs meeting the positive signal threshold can be found in Supplementary Table 2.

The subgroup analysis identified 23 positive PTs in male patients, 20 in female patients, 14 in the 18 to 64 age group, and 23 in patients aged 65 years and older. Notably, in male patients, the risk of several AEs was significantly higher with AG treatment compared to G treatment, including immune-mediated hepatitis (ROR = 23.51, 95% CI = 3.21–172.1), septic shock (ROR = 3.12, 95% CI = 1.44–6.74), gastrointestinal hemorrhage (ROR = 2.84, 95%CI = 1.3–6.19), hypertransaminasemia (ROR = 2.28, 95% CI = 1.07–4.84) and vomiting (ROR = 2.07, 95% CI = 1.37–3.12). In female patients, elevated risks were observed for fall (ROR = 9.96, 95% CI = 2.37–41.82), syncope (ROR = 7.46, 95% CI = 1.75–31.82), urinary tract infection (ROR = 6.87, 95% CI = 2.09–22.58), embolism (ROR = 3.26, 95% CI = 1.24–8.6), fatigue (ROR = 2.55, 95% CI = 1.6–4.06), peripheral neuropathy (ROR = 2.55, 95% CI = 1.53–4.26), alopecia (ROR = 2.13, 95% CI = 1.07–4.22), dyspnea (ROR = 2.25, 95% CI = 1.34–3.78), and cholangitis (ROR = 2.02, 95% CI = 1.07–3.81). Among patients aged 18 to 64 years, high-risk AEs included immune-mediated hepatitis (ROR = 16.37, 95% CI = 2.2–122.06), bile duct stenosis (ROR = 15.55, 95% CI = 2.08–116.22), and cholangitis (ROR = 3.03, 95% CI = 1.51–6.11). In elderly patients (≥ 65 years), there was an increased risk for presyncope (ROR = 24.84, 95% CI = 3.4–181.28), fall (ROR = 18.60, 95% CI = 2.53–136.97), small intestinal obstruction (ROR = 17.22, 95% CI = 2.33–127.14), muscular weakness (ROR = 3.99, 95% CI = 1.54–10.33), neurotoxicity (ROR = 3.86, 95% CI = 1.49–9.99), urinary tract infection (ROR = 3.05, 95% CI = 1.34–6.93), platelet count decreased (ROR = 2.60, 95% CI = 1.41–4.8), and decreased appetite (ROR = 2.22, 95% CI = 1.4–3.51). In the first 30 days of onset, AG treatment was associated with a higher risk of certain AEs than G treatment, including cholangitis (ROR = 7.71, 95% CI = 1.86–32.02), disseminated intravascular coagulation (ROR = 6.28, 95% CI = 1.5–26.26), atrial fibrillation (ROR = 3.77, 95% CI = 1.14–12.43), neutrophil count decreased (ROR = 3.41, 95% CI = 1.34–8.63), platelet count decreased (ROR = 2.49, 95% CI = 1.12–5.54), and abdominal pain (ROR = 2.35,

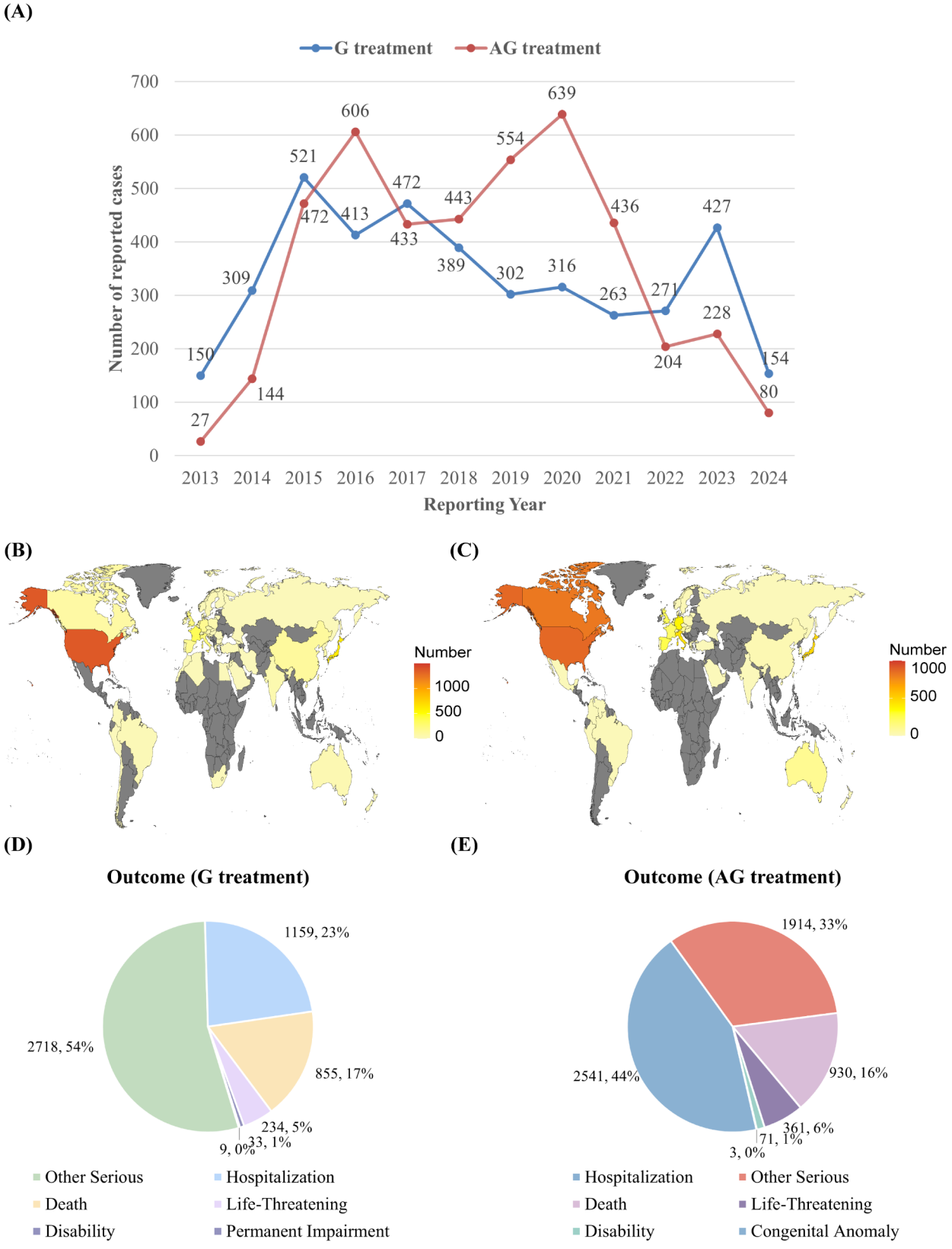

Fig. 2 Visualization of clinical characteristics associated with the two treatments. (**a**) Line plot of the number of adverse event reports over years (**b**) Worldwide distribution of case reporters in G treatment (**c**) Worldwide distribution of case reporters in AG treatment (**d**) Outcome of case reporters in G treatment (**e**) Outcome of case reporters in AG treatment. *Abbreviation* G treatment, gemcitabine monotherapy; AG treatment, gemcitabine combined with albumin-bound paclitaxel

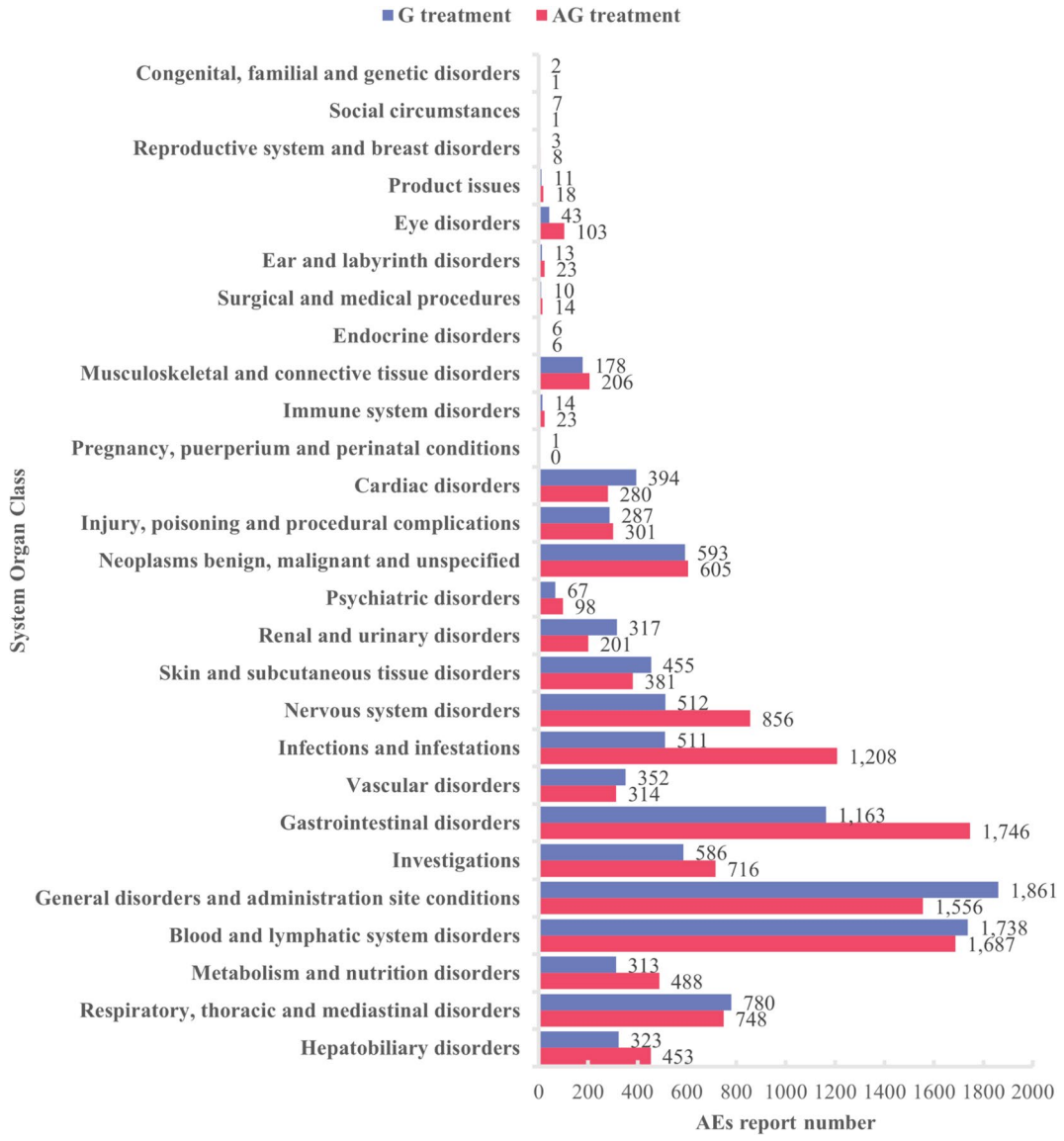

Fig. 3 The number of adverse events at the level of SOC between G and AG treatment. *Abbreviation* G treatment, gemcitabine monotherapy; AG treatment, gemcitabine combined with albumin-bound paclitaxel

95% CI = 1.2–4.62). Detailed information regarding the PTs can be found in Supplementary Tables 3–7.

TTO analysis

In the G treatment group, the major AEs of cases (48.3%) occurred within the first 30 days, totaling 372 reports. The next highest categories were 91–180 days (16.5%, 127 cases) and 31–60 days (14.8%, 114 cases), with very few cases reported after 360 days (1.6%, 12 cases) (Fig. 4a). Similarly, in the AG treatment group, 44% of cases (960 reports) occurred within the first 30 days, followed by 31–60 days (17%, 371 cases) and 91–180 days (16.5%, 359 cases). Cases reported after 360 days were minimal (3.3%, 73 cases) (Fig. 4b). The median onset time for the G treatment group was 34 days (IQR: 8-103 days), while the AG treatment group had a median onset time of 41 days (IQR: 10–104 days). A comparison of median onset times showed no statistically significant difference between the two groups ($P = 0.10$). The WSP suggests an early failure type for both groups, indicating a decline in the incidence of AEs over time (Fig. 4C and D).

The subgroup analysis of TTO evaluated differences by gender and age between the two treatment groups. In female patients, the G treatment group had a median onset time of 37 days, compared to 40 days for the AG treatment group ($P = 0.16$), indicating no significant difference. In male patients, the AG treatment group exhibited a significantly longer median onset time of 42 days compared to 27 days for the G treatment group ($P < 0.001$). Among patients aged 18–64 years, the

Table 3 Comparing safety signals of gemcitabine with or without albumin-bound paclitaxel at the PT level (The top 50 frequency of adverse drug reactions in AG treatment)

System Organ Class	PT	Number of AG treatment	Number of G treatment	ROR (95%CI)	PRR (χ^2)
Blood and lymphatic system disorders	Neutropenia	335	266	1.11 (0.94–1.3)	1.1 (1.45)
	Anaemia	316	209	1.33 (1.12–1.59)	1.32 (10.18)
	Thrombocytopenia	297	292	0.89 (0.75–1.05)	0.89 (2.04)
	Febrile neutropenia**	182	65	2.47 (1.86–3.29)	2.45 (41.59)
	Leukopenia	130	110	1.03 (0.8–1.34)	1.03 (0.07)
	Pancytopenia	75	50	1.31 (0.92–1.88)	1.31 (2.25)
	Thrombotic microangiopathy	49	300	0.14 (0.1–0.19)	0.14 (219.79)
	Disseminated intravascular coagulation**	49	20	2.15 (1.28–3.62)	2.14 (8.7)
Gastrointestinal disorders	Diarrhoea	254	116	1.94 (1.55–2.42)	1.92 (35.49)
	Vomiting	226	106	1.88 (1.49–2.37)	1.87 (29.44)
	Nausea	224	138	1.43 (1.15–1.77)	1.42 (10.81)
	Abdominal pain*	193	76	2.24 (1.72–2.93)	2.22 (37.12)
	Constipation*	86	26	2.91 (1.87–4.51)	2.9 (24.89)
	Colitis**	56	22	2.23 (1.36–3.66)	2.23 (10.73)
	Gastrointestinal haemorrhage	55	53	0.91 (0.62–1.33)	0.91 (0.25)
	Stomatitis*	53	12	3.88 (2.07–7.26)	3.87 (20.85)
	Upper gastrointestinal haemorrhage**	46	9	4.49 (2.2–9.17)	4.47 (20.35)
	Ascites	46	53	0.76 (0.51–1.13)	0.76 (1.88)
General disorders and administration site conditions	Pyrexia	318	141	2 (1.64–2.44)	1.97 (47.92)
	Fatigue	221	111	1.76 (1.4–2.21)	1.74 (23.74)
	Asthenia	145	90	1.42 (1.09–1.84)	1.41 (6.7)
	Oedema peripheral	113	73	1.36 (1.01–1.83)	1.35 (4.16)
	General physical health deterioration	94	49	1.68 (1.19–2.38)	1.68 (8.9)
Infections and infestations	Sepsis**	224	71	2.79 (2.14–3.65)	2.76 (61.38)
	Pneumonia**	168	62	2.39 (1.78–3.2)	2.37 (36.3)
	Biliary tract infection**	69	3	20.24 (6.37–64.33)	20.13 (52.44)
	Septic shock	54	32	1.48 (0.95–2.29)	1.48 (3.11)
	Infection*	49	20	2.15 (1.28–3.62)	2.14 (8.7)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	132	61	1.9 (1.4–2.58)	1.89 (17.76)
	Interstitial lung disease	94	121	0.68 (0.52–0.89)	0.68 (8.04)
	Pneumonitis	84	72	1.02 (0.74–1.4)	1.02 (0.02)
	Pleural effusion	73	94	0.68 (0.5–0.92)	0.68 (6.25)
	Pulmonary embolism	54	59	0.8 (0.55–1.16)	0.8 (1.4)
Nervous system disorders	Peripheral neuropathy	188	123	1.34 (1.07–1.69)	1.34 (6.43)
	Neurotoxicity	59	30	1.72 (1.11–2.68)	1.72 (6.04)
	Cerebrovascular accident**	58	16	3.18 (1.83–5.54)	3.17 (18.72)
	Paraesthesia*	49	6	7.17 (3.07–16.75)	7.15 (28.34)
Investigations	Platelet count decreased	96	44	1.92 (1.34–2.74)	1.91 (13.16)
	Neutrophil count decreased*	87	32	2.39 (1.59–3.59)	2.38 (18.81)
	White blood cell count decreased	50	25	1.75 (1.08–2.84)	1.75 (5.38)
	Weight decreased	46	39	1.03 (0.67–1.58)	1.03 (0.02)
Metabolism and nutrition disorders	Decreased appetite	125	67	1.64 (1.22–2.21)	1.63 (10.79)
	Dehydration*	114	45	2.23 (1.58–3.15)	2.22 (21.72)
Hepatobiliary disorders	Cholangitis	108	51	1.86 (1.33–2.6)	1.85 (13.71)
	Hypertransaminasaemia	49	22	1.95 (1.18–3.23)	1.95 (7.04)
Skin and subcutaneous tissue disorders	Alopecia	91	44	1.82 (1.27–2.61)	1.81 (10.82)
	Rash	53	70	0.66 (0.46–0.95)	0.66 (5.21)
Renal and urinary disorders	Acute kidney injury	86	94	0.8 (0.6–1.07)	0.8 (2.24)

Table 3 (continued)

System Organ Class	PT	Number of AG treatment	Number of G treatment	ROR (95%CI)	PRR (χ^2)
Vascular disorders	Hypotension*	64	16	3.51 (2.03–6.08)	3.5 (22.95)
Cardiac disorders	Atrial fibrillation**	49	15	2.87 (1.61–5.11)	2.86 (13.92)

Abbreviation Asterisks (*) indicate statistically significant signals in the algorithm; two asterisks (**) further indicate Important medical events (IMEs); ROR, reporting odds ratio; PRR, proportional reporting ratio; PT, preferred term; 95%CI, 95% confidence interval; G treatment, gemcitabine monotherapy; AG treatment, gemcitabine combined with albumin-bound paclitaxel

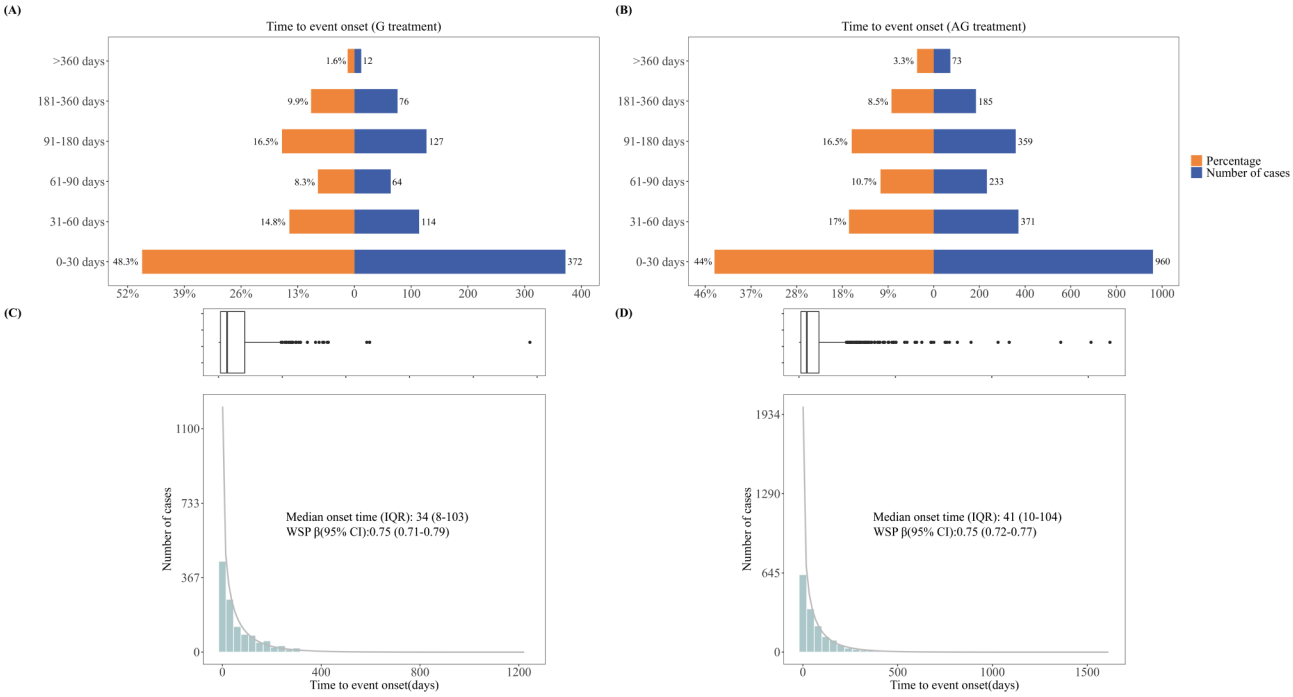

Fig. 4 The time to onset and weibull distribution analysis of AEs among two treatment groups. (**a**) Time to onset for G treatment-related AEs (**b**) Time to onset for AG treatment-related AEs (**c**) The box plot, histogram and weibull distribution of onset time for G treatment-related AEs (**d**) The box plot, histogram and weibull distribution of onset time for AG treatment-related AEs. *Abbreviations* AEs, adverse events; WSP, weibull shape parameter; 95% CI, confidence interval; IQR, interquartile range; G treatment, gemcitabine monotherapy; AG treatment, gemcitabine combined with albumin-bound paclitaxel

Table 4 Multivariable logistic regression models of fatal outcomes (Death)

Variable	Number of cases	Adjusted OR (95%CI)	*P*
Gender			
Female	1104	1.00 (Reference)	
Male	1508	1.42 (1.15–1.76)	< 0.01
Age(years)			
< 65	1036	1.00 (Reference)	
≥ 65	1576	1.36 (1.10–1.69)	< 0.01
Weight (kg)			
< 80	2000	1.00 (Reference)	
80–100	496	0.62 (0.46–0.82)	< 0.01
> 100	116	0.90 (0.54–1.47)	0.66
Drug therapy			
G treatment	734	1.00 (Reference)	
AG treatment	1878	1.18 (0.94–1.49)	0.16

Abbreviation OR: odds ratio; CI: confidence interval; G treatment, gemcitabine monotherapy; AG treatment, gemcitabine combined with albumin-bound paclitaxel; $p < 0.05$ were considered statistically significant

median onset times were 32 days for G treatment and 45 days for AG treatment ($P = 0.13$). In the older subgroup (≥ 65 years), the median onset time for G treatment was 28 days, compared to 38 days for AG treatment ($P = 0.11$). No significant differences in TTO were observed between the two treatments in either age group. The Weibull distribution analysis indicated that all subgroups exhibited an early failure type, with further details provided in Supplementary Tables 8 and Supplementary Fig. 1.

Logistic regression analysis

Table 4 summarizes the multivariable logistic regression models assessing factors associated with fatal outcomes (Death) in patients receiving treatment. Males had a significantly higher risk of death than females, which revealed an adjusted OR of 1.42 (95% CI = 1.15–1.76, $P < 0.01$), indicating that male patients are 42% more likely to experience fatal outcomes. Elderly patients also demonstrated a higher likelihood of death, with an

adjusted OR of 1.36 (95% CI = 1.10–1.69, $P < 0.01$). Conversely, patients weighing between 80 and 100 kg had a reduced risk of death, with an adjusted OR of 0.62 (95% CI = 0.46–0.82, $P < 0.01$). Patients weighing over 100 kg and the treatment groups were not significantly associated with death. Univariable analysis results are in Supplementary Table 9.

Discussion

Previous research on treating PC with gemcitabine or albumin-bound paclitaxel has primarily focused on clinical trials and literature reviews. Comparative studies on post-marketing safety remain limited. Therefore, we utilized the FAERS database to comprehensively investigate post-marketing AERs associated with these two treatment regimens, aiming to guide their clinical application. By analyzing data from the third quarter of 2013 to the second quarter of 2024, we compared the risk of AEs associated with G and AG treatments in patients with pancreatic cancer. We identified 17 safety signals (PTs) among the top 50 most common AEs, of which 9 were classified as IMEs. Gender and age were risk factors for fatal outcomes through logistic regression analysis. Additionally, subgroup and TTO analyses revealed differences in the risk of AEs among various populations and periods, offering clinicians new monitoring directions and potential risk indicators.

The study revealed specific trends related to gender and age. In both treatment groups, a higher proportion of males experienced related AEs, with rates of 54.1% and 37.0%, respectively. The largest number of reports came from elderly patients, reflecting the high incidence of PC within this demographic. According to the American Cancer Society, PC incidence is higher in males than females, and age is a significant risk factor, with approximately two-thirds of patients being 65 or older [16]. In the present study, death ratios in outcomes were comparable between the two treatment groups, at 17% and 16%, respectively. Further logistic regression analysis showed no significant difference between the two treatments in terms of fatal outcomes, suggesting that AG treatment may be safe and tolerable. However, males and elderly patients were identified as high-risk groups for fatal outcomes, emphasizing the need for clinicians to remain vigilant and conduct risk-benefit assessments for these populations [17].

As observed in previous studies, myelosuppression is a common hematologic adverse reaction associated with gemcitabine or albumin-bound paclitaxel, manifesting as neutropenia, leukopenia, anemia, and thrombocytopenia [18, 19]. To prevent complications such as infections, physicians should regularly monitor hematologic parameters. Current management strategies include supportive therapies, such as granulocyte colony-stimulating factor (G-CSF) and erythropoietin (EPO) [20, 21]. While gemcitabine effectively inhibits cancer cell proliferation, it also impacts rapidly proliferating normal cells, leading to myelosuppression [22]. This condition results from gemcitabine's effects on hematopoietic stem and progenitor cells (HSPCs), as evidenced by reduced cell proliferation and alterations in gene expression related to bone marrow cell proliferation and differentiation [23]. In mouse models, gemcitabine has demonstrated cytotoxic effects on bone marrow, increasing the frequency of micronuclei and chromosomal aberrations [24]. Albumin-bound paclitaxel, a nanoparticle formulation of paclitaxel bound to human serum albumin, may enhance gemcitabine's intratumoral concentration by reducing cytidine deaminase (CDA) levels through reactive oxygen species (ROS) induction [25]. Although AG treatment has shown survival benefits for PC patients, clinical trials have reported higher rates of febrile neutropenia and neutropenia in the AG treatment group compared to the G treatment group (3% vs. 1% and 38% vs. 27%, respectively) [7]. In this study, disproportionality analysis further confirmed that combination therapy increases the risk of neutropenia and febrile neutropenia. These findings highlight the importance of monitoring AEs during AG treatment to ensure patient safety.

Gastrointestinal disorders are the most common SOC of AEs associated with AG treatment in patients with PC, with a total of 1746 reported cases. Consistent with previous studies, gastrointestinal reactions are frequent side effects of cancer chemotherapy [26]. The underlying mechanisms involve factors such as gut microbiota dysbiosis and inflammatory responses, leading to treatment interruptions, dose reductions, or even discontinuation, negatively affecting patient outcomes [27]. According to our findings, diarrhea, vomiting, and nausea were the most frequently reported AEs. However, compared to G treatment, AG treatment was associated with a significantly higher risk of abdominal pain, constipation, colitis, stomatitis, and upper gastrointestinal hemorrhage. The synergistic effects of combination therapy may increase cytotoxicity in the gastrointestinal tract, potentially explaining the elevated risk of these AEs. The study has found that the use of probiotics can improve gut microbial composition, thereby alleviating side effects [28]. Gastrointestinal toxicity remains a challenge, underscoring the need for further research and the development of effective management strategies to mitigate these AEs.

Compared to G treatment, AG treatment may increase the risk of atrial fibrillation (AF) (ROR = 2.87, 95% CI = 1.61–5.11), a relatively rare AEs in the cardiac disorders category. Recent reports of gemcitabine-associated AF underscore the importance of monitoring for symptoms such as dyspnea and palpitations after infusion [29]. While AG treatment offers efficacy benefits,

vigilant monitoring of potential AEs, including cardiac events, is essential for patient safety. Neurological AEs are also notable; previous studies indicate a higher incidence of peripheral neuropathy in PC patients on AG treatment group(17% vs. 1%), possibly due to paclitaxel's impact on microtubule stability, which causes axonal damage and neuropathy symptoms [7, 30]. Although effective measures are limited, IL-20 inhibition may alleviate paclitaxel-induced neurotoxicity while preserving its anticancer effects, suggesting a potential therapeutic approach [31]. Our study found reported frequencies of peripheral neuropathy to be 188 in the AG treatment group and 123 in the G treatment group, with no significant difference in overall risk. However, stratified analysis indicates a higher risk of peripheral neuropathy in female patients receiving AG treatment. Further subgroup analysis reveals that elderly patients show increased risks of presyncope ((ROR = 24.84, 95% CI = 3.4–181.28) and fall (ROR = 18.60, 95% CI = 2.53–136.97). Differences in weight, metabolism, and changes in metabolic enzymes that affect pharmacokinetics across different ages and genders may help explain the biological mechanisms underlying AEs [32]. Therefore, age- and gender-specific analyses in pharmacovigilance are crucial for effectively addressing drug safety in diverse patient populations [33, 34].

In this study, immune-mediated hepatitis (IMH) was identified as a significant AE associated with AG treatment. Subgroup analysis revealed that male patients had the highest risk of developing IMH (ROR = 23.51, 95% CI = 3.21–172.1). IMH is an inflammatory liver injury caused by aberrant immune responses [35]. Its underlying mechanism is likely related to immune dysregulation induced by chemotherapy [36]. One study demonstrated that gemcitabine combined with avelumab may activate specific immune cells, such as T cells or natural killer cells, leading to autoimmune attacks on hepatocytes [37]. In combination therapy, this effect may be further amplified by chemotherapy-related hepatic inflammation [38], particularly in patients with pre-existing liver impairment or increased metabolic burden. Key clinical manifestations include significantly elevated liver enzymes, jaundice, and, in severe cases, liver failure. So, close monitoring of liver function is essential for patients receiving AG treatment to detect and manage potential IMH early.

Biliary sepsis was another notable AE identified in AG treatment (ROR = 3.07, 95% CI = 1.01–9.32). Evidence from previous studies showed that biliary sepsis occurred only with combination therapy, such as gemcitabine with cisplatin, and not with monotherapy, further supporting the link between combination chemotherapy and biliary infections [39]. This AE is likely associated with chemotherapy-induced immunosuppression and neutropenia, as indicated by the strong signal for febrile neutropenia in AG treatment in our study. Additionally, pancreatic cancer patients often experience biliary obstruction or require biliary stents, increasing their susceptibility to biliary infections [40].

In terms of gastrointestinal infections, this study identified a relatively strong association between infectious enterocolitis and AG treatment (ROR = 8.19, 95% CI = 2.49–26.93). This condition is commonly attributed to chemotherapy-induced immunosuppression and compromised intestinal barrier function [41]. Moreover, a randomized controlled trial demonstrated a higher incidence of Clostridium difficile infection (CDI) in patients treated with AG compared to those receiving AG combined with pharmacologic ascorbate [42]. This may be due to disruption of intestinal epithelial integrity, particularly through the cell division-inhibiting effects of paclitaxel [43], which can weaken the intestinal barrier and facilitate CDI colonization and infection. The infection-related AEs identified in AG treatment significantly impact patient treatment and prognosis. To mitigate these risks, comprehensive pre-treatment assessments of intestinal integrity should be conducted. For high-risk patients, enhanced infection prevention and immune management are essential to ensure treatment safety and efficacy [44].

This study also analyzed the TTO of AEs and established a Weibull distribution model to predict occurrence trends, facilitating the development of an effective monitoring timeline for ADRs. The results indicated that most AEs occurred within the first month of treatment, with no significant difference in median TTO between the groups. Given that the majority of AEs in both treatment groups were concentrated within the first 30 days, we focused specifically on AERs from this period and conducted risk comparisons at the PT level. Significant AEs with notable risk differences included disseminated intravascular coagulation, neutropenia, thrombocytopenia, abdominal pain, cholangitis, and atrial fibrillation. These findings highlight the importance of early monitoring in identifying and managing potential AEs, providing valuable guidance for risk management during treatment. Early intervention, such as dosage adjustments and supportive care strategies [45, 46], can enhance medication safety and improve patient outcomes.

However, this study also has several important limitations. Firstly, the FAERS database consists of spontaneous reports from consumers, physicians, and pharmacists, which may lead to selection bias or data underreporting, thereby limiting our ability to conduct an in-depth analysis of the relationship between drug usage and AEs [47, 48]. Secondly, the data primarily originate from Europe and the United States, which may introduce geographical reporting bias. Therefore, future studies should include data from a broader range of regions to enhance the

generalizability of the findings. Lastly, while this study focuses on specific drugs and their indications, thus enhancing the specificity of the results, it is important to note that reports in the FAERS database cannot establish causal relationships between drugs and AEs; they can only provide preliminary signals of potential risks. Further research is needed to validate the findings of this study. Subsequent studies should incorporate more extensive datasets, including electronic medical records and longitudinal research, to enhance the reliability of drug safety evaluations.

Conclusion

In conclusion, this study addresses the research gap in real-world safety evaluations of the AG treatment for pancreatic cancer. Utilizing FAERS data from 2013 to 2024 and pharmacovigilance algorithms, we compared the safety profiles of G and AG treatments. The analysis identified a higher risk of AEs in the AG group, particularly in blood, gastrointestinal, cardiac, and neurological events, with a pronounced impact on male and elderly patients. These findings highlight the need for AEs monitoring in high-risk groups to improve treatment safety and AEs management strategy in patients. Given the limitations of the FAERS database, more rigorous studies are needed to validate our findings.

Abbreviations

PC	Pancreatic Cancer
G	Gemcitabine
AG	Albumin-bound Paclitaxel with Gemcitabine
FDA	Food and Drug Administration
FAERS	FDA Adverse Event Reporting System
AEs	Adverse Events
TTO	Time to Onset
ROR	Reporting Odds Ratio
PRR	Proportional Reporting Ratio
PT	Preferred Term
SOC	System Organ Class
IMEs	Important Medical Events
OR	Odds Ratio
IQR	Interquartile Range
WSP	Weibull Shape Parameter
EMA	European Medicines Agency

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40360-025-00884-5.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

PJ performed data analysis and wrote the first draft. KZ and DP prepared figures and tables. BZ and ZW designed the project and revised the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable.

Data availability

The datasets analyzed during the current study are available online at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html.

Declarations

Ethics approval and consent to participate

All data used in this study were publicly available and anonymized. Thus, no ethical approval or informed consent was required.

Clinical trial number

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Hepatobiliary Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

Received: 21 November 2024 / Accepted: 27 February 2025
Published online: 19 March 2025

References

1. Halbrook CJ, Lyssiotis CA, Pasca di Magliano M, Maitra A. Pancreatic cancer: advances and challenges. Cell. 2023;186:1729–54.
2. Gyawali B, Booth CM. Treatment of metastatic pancreatic cancer: 25 years of innovation with little progress for patients. Lancet Oncol. 2024;25:167–70.
3. Burris HA, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol. 1997;15:2403–13.
4. Bria E, Milella M, Gelibter A, Cuppone F, Pino MS, Ruggeri EM, et al. Gemcitabine-based combinations for inoperable pancreatic cancer: have we made real progress? A meta-analysis of 20 phase 3 trials. Cancer. 2007;110:525–33.
5. Li Q, Yan H, Liu W, Zhen H, Yang Y, Cao B. Efficacy and safety of gemcitabine-fluorouracil combination therapy in the management of advanced pancreatic cancer: a meta-analysis of randomized controlled trials. PLoS ONE. 2014;9:e104346.
6. Thota R, Pauff JM, Berlin JD. Treatment of metastatic pancreatic adenocarcinoma: a review. Oncol (Williston Park). 2014;28:70–4.
7. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369:1691–703.
8. Duggirala HJ, Tonning JM, Smith E, Bright RA, Baker JD, Ball R, et al. Use of data mining at the food and drug administration. J Am Med Inf Assoc. 2016;23:428–34.
9. Harpaz R, DuMochel W, Shah NH. Big data and adverse drug reaction detection. Clin Pharmacol Ther. 2016;99:268–70.
10. Sakaeda T, Tamon A, Kadoyama K, Okuno Y. Data mining of the public version of the FDA adverse event reporting system. Int J Med Sci. 2013;10:796–803.
11. Morley G. Adverse event reporting: A brief overview of MedDRA. Med Writ. 2014;23:113–6.
12. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. Pharmacoepidemiol Drug Saf. 2004;13:519–23.
13. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. Pharmacoepidemiol Drug Saf. 2001;10:483–6.
14. Chen Y, Guo JJ, Steinbuch M, Lin X, Buncher CR, Patel NC. Comparison of sensitivity and timing of early signal detection of four frequently used signal

detection methods: an empirical study based on the US FDA adverse event reporting system database. Pharm Med. 2008;22:359–65.
15. Kinoshita S, Hosomi K, Yokoyama S, Takada M. Time-to-onset analysis of amiodarone-associated thyroid dysfunction. J Clin Pharm Ther. 2020;45:65–71.
16. Cancer Facts & Figures 2023. 1930.
17. Freedman AN, Yu B, Gail MH, Costantino JP, Graubard BI, Vogel VG, et al. Benefit/risk assessment for breast cancer chemoprevention with raloxifene or Tamoxifen for women age 50 years or older. J Clin Oncol. 2011;29:2327–33.
18. Cecco S, Aliberti M, Baldo P, Giacomin E, Leone R. Safety and efficacy evaluation of albumin-bound Paclitaxel. Expert Opin Drug Saf. 2014;13:511–20.
19. Corty RW, Langworthy BW, Fine JP, Buse JB, Sanoff HK, Lund JL. Antibacterial use is associated with an increased risk of hematologic and Gastrointestinal adverse events in patients treated with gemcitabine for stage IV pancreatic cancer. Oncologist. 2020;25:579–84.
20. Gascón P, Awada A, Karihtala P, Lorenzen S, Minichsdorfer C. Optimal use of granulocyte colony-stimulating factor prophylaxis to improve survival in cancer patients receiving treatment: an expert view. Wien Klin Wochenschr. 2024;136:362–8.
21. Link H. Hematopoietic growth factors in the management of Anemia and febrile neutropenia. Breast Care. 2019;14:93–8.
22. Björn N, Sigurgeirsson B, Svedberg A, Pradhananga S, Brandén E, Koyi H, et al. Genes and variants in hematopoiesis-related pathways are associated with gemcitabine/carboplatin-induced thrombocytopenia. Pharmacogenomics J. 2020;20:179–91.
23. Björn N, Jakobsen I, Lotfi K, Gréen H. Single-cell RNA sequencing of hematopoietic stem and progenitor cells treated with gemcitabine and carboplatin. Genes. 2020;11:549.
24. Aydemir N, Bilaloğlu R. Genotoxicity of two anticancer drugs, gemcitabine and Topotecan, in mouse bone marrow in vivo. Mutat Research/Genetic Toxicol Environ Mutagen. 2003;537:43–51.
25. Frese KK, Neesse A, Cook N, Bapiro TE, Lolkema MP, Jodrell DI, et al. nab-Paclitaxel potentiates gemcitabine activity by reducing cytidine deaminase levels in a mouse model of pancreatic cancer. Cancer Discov. 2012;2:260–9.
26. Aprile G, Rihawi K, De Carlo E, Sonis ST. Treatment-related Gastrointestinal toxicities and advanced colorectal or pancreatic cancer: A critical update. World J Gastroenterol. 2015;21:11793.
27. He Y, Zheng J, Ye B, Dai Y, Nie K. Chemotherapy-induced Gastrointestinal toxicity: pathogenesis and current management. Biochem Pharmacol. 2023:115787.
28. Fernandes C, Miranda MCC, Roque CR, Paguada ALP, Mota CAR, Florêncio KGD, et al. Is there an interplay between environmental factors, microbiota imbalance, and Cancer Chemotherapy-Associated intestinal mucositis?? Pharmaceuticals. 2024;17:1020.
29. Ferrari D, Carbone C, Codecà C, Fumagalli L, Gilardi L, Marussi D, et al. Gemcitabine and atrial fibrillation: a rare manifestation of chemotherapy toxicity. Anticancer Drugs. 2006;17:359–61.
30. Klein I, Lehmann HC. Pathomechanisms of paclitaxel-induced peripheral neuropathy. Toxics. 2021;9:229.
31. Chen L-H, Yeh Y-M, Chen Y-F, Hsu Y-H, Wang H-H, Lin P-C, et al. Targeting interleukin-20 alleviates paclitaxel-induced peripheral neuropathy. Pain. 2020;161:1237–54.
32. De Francia S, Mancardi D, Berchialla P, Armando T, Storto S, Allegra S, et al. Gender-specific side effects of chemotherapy in pancreatic cancer patients. Can J Physiol Pharmacol. 2022;100:371–7.
33. Shen J, Hu R, Lin A, Jiang A, Tang B, Liu Z, et al. Characterization of second primary malignancies post CAR T-cell therapy: real-world insights from the two global pharmacovigilance databases of FAERS and vigibase. EClinicalMedicine. 2024;73:102684.
34. Liu Q, Cui Z, Deng C, Yang C, Shi T. A real-world pharmacovigilance analysis of adverse events associated with Irbesartan using the FAERS and JADER databases. Front Pharmacol. 2024;15:1485190.
35. Hercun J, Vincent C, Bilodeau M, Lapierre P. Immune-Mediated hepatitis during immune checkpoint inhibitor cancer immunotherapy: lessons from autoimmune hepatitis and liver immunology. Front Immunol. 2022;13:907591.
36. Lasagna A, Sacchi P. The ABC of Immune-Mediated hepatitis during immunotherapy in patients with cancer: from pathogenesis to multidisciplinary management. Cancers (Basel). 2024;16:795.
37. Kim M, Kim YJ, Suh KJ, Kim SH, Kim JE, Jeong J, et al. Phase 2 trial of avelumab in combination with gemcitabine in advanced leiomyosarcoma as a second-line treatment (EAGLES, Korean Cancer study group UN18-09). Cancer. 2025;131:e35609.
38. Tykodi SS, Gordan LN, Alter RS, Arrowsmith E, Harrison MR, Percent I, et al. Safety and efficacy of nivolumab plus ipilimumab in patients with advanced non-clear cell renal cell carcinoma: results from the phase 3b/4 checkmate 920 trial. J Immunother Cancer. 2022;10:e003844.
39. Siebenhüner AR, Seifert H, Bachmann H, Seifert B, Winder T, Feilchenfeldt J, et al. Adjuvant treatment of resectable biliary tract cancer with cisplatin plus gemcitabine: A prospective single center phase II study. BMC Cancer. 2018;18:72.
40. Teränen V, Nissinen S, Roine A, Antila A, Siiki A, Vaalavuo Y, et al. Bile-volatile organic compounds in the diagnostics of pancreatic cancer and biliary obstruction: A prospective proof-of-concept study. Front Oncol. 2022;12:918539.
41. Vogel A, Saborowski A, Wenzel P, Wege H, Folprecht G, Kretzschmar A, et al. Nanoliposomal Irinotecan and fluorouracil plus leucovorin versus fluorouracil plus leucovorin in patients with cholangiocarcinoma and gallbladder carcinoma previously treated with gemcitabine-based therapies (AIO NALIRICC): a multicentre, open-label, randomised, phase 2 trial. Lancet Gastroenterol Hepatol. 2024;9.
42. Bodeker KL, Smith BJ, Berg DJ, Chandrasekharan C, Sharif S, Fei N, et al. A randomized trial of Pharmacological ascorbate, gemcitabine, and nab-paclitaxel for metastatic pancreatic cancer. Redox Biol. 2024;77:103375.
43. Shichi Y, Gomi F, Sasaki N, Nonaka K, Arai T, Ishiwata T. Epithelial and mesenchymal features of pancreatic ductal adenocarcinoma cell lines in Two- and Three-Dimensional cultures. J Pers Med. 2022;12:746.
44. Monroy-Iglesias MJ, Dolly S, Sarker D, Thillai K, Van Hemelrijck M, Santaolalla A. Pancreatic Cancer exposome profile to aid early detection and inform prevention strategies. J Clin Med. 2021;10:1665.
45. Chang C, Li X, Cao D. Combination of gemcitabine, nab-paclitaxel, and S-1(GAS) as the first-line treatment for patients with locally advanced or advanced pancreatic ductal adenocarcinoma: study protocol for an open-label, single-arm phase I study. BMC Cancer. 2021;21:545.
46. Rapoport BL, Cooksley T, Johnson DB, Anderson R. Supportive care for new cancer therapies. Curr Opin Oncol. 2021;33:287–94.
47. Maciá-Martínez M-A, De Abajo FJ, Roberts G, Slattery J, Thakrar B, Wisniewski AFZ. An empirical approach to explore the relationship between measures of disproportionate reporting and relative risks from analytical studies. Drug Saf. 2016;39:29–43.
48. Montastruc J-L, Sommet A, Lacroix I, Olivier P, Durrieu G, Damase-Michel C, et al. Pharmacovigilance for evaluating adverse drug reactions: value, organization, and methods. Joint Bone Spine. 2006;73:629–32.

Publisher's note