Characteristics and outcomes of gemcitabine-associated pulmonary hypertension

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Abstract

Background Despite its known cardiac and lung toxicities, the chemotherapy drug gemcitabine has only rarely been associated with pulmonary hypertension (PH), and the underlying mechanism remains unclear. The objective of the present study was to assess the association between gemcitabine and PH.

Methods We identified incident cases of precapillary PH confirmed by right heart catheterisation in patients treated with gemcitabine from the French PH Registry between January 2007 and December 2022. The aetiology, clinical, functional, radiological and haemodynamic characteristics of PH were reviewed at baseline and during follow-up. A pharmacovigilance disproportionality analysis was conducted using the World Health Organization (WHO) pharmacovigilance database.

Results We identified nine cases of pulmonary arterial hypertension, either induced (in eight patients) or exacerbated (in one patient) by gemcitabine. Patients exhibited severe precapillary PH, with a median mean pulmonary arterial pressure of 40 (range 26–47) mmHg, a cardiac index of 2.4 (1.6–3.9) $L \cdot min^{-1} \cdot m^{-2}$ and a pulmonary vascular resistance of 6.3 (3.1–12.6) Wood units. The median time from the initiation of gemcitabine to the onset of PH was 7 (4–50) months, with patients receiving a median of 16 (6–24) gemcitabine injections. Six patients showed clinical improvement upon discontinuation of gemcitabine. In the WHO pharmacovigilance database, we identified a significant signal with 109 cases reporting at least one adverse event related to PH with gemcitabine.

Conclusion Both clinical cases and pharmacovigilance data substantiate a significant association between gemcitabine use and the onset or worsening of precapillary PH. The observed improvement following the discontinuation of treatment underscores the importance of PH screening in gemcitabine-exposed patients experiencing unexplained dyspnoea.

Introduction

Gemcitabine is a pyrimidine antimetabolite commonly used in oncology to treat various types of solid cancer [1]. It provides antitumour cytotoxic activity by inhibiting the S-phase of the cell cycle through its

active metabolites, deoxy-cytidine di- and triphosphate. Gemcitabine treatment is indicated in locally advanced or metastatic bladder, pancreatic [2], ovarian and nonsmall cell lung cancer [3], as well as in locally advanced, metastatic or relapsed inoperable breast cancer. It is an intravenously administered chemotherapy drug with systemic activity, often well tolerated but with potentially serious and fatal side-effects [4–7]. Pulmonary toxicities have been described in 2–40% of patients exposed to gemcitabine [8–10]. This toxicity may be reversible for dyspnoea, acute non-cardiogenic pulmonary oedema [11], hypersensitivity pneumonitis [12], eosinophilic pneumonitis [13], acute or chronic fibrosing interstitial lung disease [14, 15], pleural effusion, bronchospasm and diffuse alveolar haemorrhage. However, in all these reports the causality of gemcitabine is difficult to assess, particularly in the suspected hypersensitivity pneumonitis.

Pulmonary arterial hypertension (PAH) is a rare condition with a high mortality rate, characterised by increased blood pressure in the pulmonary vasculature [16]. The consequence is right heart failure with a severe and unfavourable prognosis [17]. PAH can be associated with various conditions including connective tissue diseases, human immunodeficiency virus infection, portal hypertension, congenital heart disease, genetic predisposition, and exposure to certain toxins or drugs. To date, a variety of drugs have been associated with the development of PAH, including dasatinib, amphetamines (aminorex, fenfluramine, dexfenfluramine, benfluorex) and recreational drugs (methamphetamine) as well as chemotherapies such as mitomycin [18].

Onset of pulmonary hypertension (PH) in patients exposed to gemcitabine has seldom been reported in isolated case reports. However, the specific mechanisms triggering this condition are not well understood. In some reports, this type of PH has been categorised as PAH [19, 20], while others have identified it as pulmonary veno-occlusive disease (PVOD) [21–23].

In this context, our objective was to delineate the characteristics and follow-up of cases of gemcitabine-associated PAH confirmed by right heart catheterisation (RHC), identified in the French PH Registry. Furthermore, we aimed to analyse cases of PH or associated symptoms reported with gemcitabine usage in the World Health Organization's (WHO) pharmacovigilance database.

Methods

Patients

We reviewed all cases of precapillary PH in patients from the French PH Registry and the French pharmacovigilance database (VIGIAPATH) programme who were treated with gemcitabine from January 2007 to December 2022.

The criteria for inclusion in our series were as follows: adult patients exposed to gemcitabine with a diagnosis of PH confirmed by RHC, and patients with clinical and/or haemodynamic worsening of pre-existing PH after exposure to gemcitabine. In the French PH Registry, these patients were classified as PAH associated with drugs exposure. The diagnosis of precapillary PH was made in accordance with the international guidelines that were effective at the time of the PH diagnosis and the patient's inclusion in the registry. These criteria included a mean pulmonary artery pressure (mPAP) $\geqslant$25 mmHg, pulmonary artery wedge pressure (PAWP) $\leqslant$15 mmHg and pulmonary vascular resistance (PVR) >3 Wood units [17]. Exclusion criteria were other causes of PH and other etiologies of PAH. The registry was established in accordance with French bioethics laws (Commission Nationale de l'Informatique et des Libertés (842063), and all patients gave their informed consent to participate in this registry. All incident cases of gemcitabine-associated PH were reviewed by two pulmonologists (P. Mouillot, N. Favrolt). The date of diagnosis of PH was defined as the date of the first RHC.

Pharmacovigilance disproportionality analysis

In June 2023, we extracted all cases reporting adverse events belonging to the Standardised MedDRA Query (SMQ) PH (narrow) with gemcitabine considered as suspect, in the WHO pharmacovigilance database, Vigibase®. SMQs are internationally validated, predetermined collections of MedDRA terms grouped together and associated with the same disease, allowing for high-sensitivity searches (*e.g.* PAH, right ventricular failure, acute cor pulmonale, tricuspid valve incompetence). As performed in previous pharmacovigilance analyses by our team on PH, to limit confounding by indication we restricted the comparator group to antineoplastic drugs and we excluded competitors to limit potential masking effects (*i.e.* associated with >5% of adverse events reported with gemcitabine or with >5% of adverse event of interest) [23, 24]. The protocol of the disproportionality analysis was pre-registered on Open Science Framework (https://osf.io/9rt5s/) and reported according to READUS-PV (https://readus-statement.org/).

Clinical, functional, radiological and haemodynamic evaluation

We collected the chemotherapy regimen, number of cycles of gemcitabine treatment, treatment indication, cancer status at the time of PH diagnosis, time between the first or the last gemcitabine injection and PH diagnosis. New York Heart Association (NYHA) functional class, brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) blood levels were collected. Arterial blood gases and pulmonary function tests, including partial pressure of oxygen (P_{aO_2}), partial pressure of carbon dioxide (P_{aCO_2}), forced expiratory volume in 1 s (FEV_1), total lung capacity (TLC) and diffusion capacity of carbon monoxide (D_{LCO}) corrected for haemoglobin concentration were collected. Chest computed tomography (CT) scans obtained at the time of diagnosis were reviewed for all subjects. CT images were systematically reviewed for signs of PVOD, thromboembolic or interstitial lung disease (ILD). The haemodynamic parameters recorded for RHC were mPAP, PAWP and right atrial pressure (RAP). Cardiac output (CO) was measured by the standard thermodilution technique. The cardiac index was calculated by dividing the CO by the body surface area. PVR was calculated as PVR = (mPAP – PAWP)/CO and expressed in Wood units [17].

Patient follow-up

We retrospectively collected follow-up data for all patients. Clinical, functional and haemodynamic data were reported during follow-up divided into three periods: 0–3 months, 3–10 months and after 10 months. Overall survival was evaluated according to the date of death or was censored at the date of the last update. We defined clinical improvement as a decrease in NYHA functional class and clinical worsening as an increase in NYHA functional class or persistence of NYHA class IV.

Statistical analysis

Variables are presented as medians (min–max) for quantitative variables and as n (%) for categorical variables. Overall survival was estimated by the Kaplan–Meier method. The end date of follow-up was 1 March 2023. We performed disproportionality analyses using the Bayesian Information Component to compare the proportion of cases reported with gemcitabine with the proportion of adverse events of interest reported in a comparator group. Signal of disproportionate reporting was considered significant if the lower boundary of the 95% credibility interval of the information component (IC025) was superior to 0 [25, 26]. Lastly, to identify syndrome of co-reported adverse events we used a new method developed by Fusaroli and colleagues [27] using network analysis coupled with a clustering approach. Briefly, all selected reports were converted to binary data (*i.e.*, presence 1 or absence 0 of each event in each report), and the weight of the links was calculated as the partial correlation between each pair of variables (nodes) conditioning on all other variables in the network. The LASSO (least shrinkage and selection operator) was used to remove small-amplitude links, thus obtaining a low rate of false positives at the expense of losing weak true associations. Finally, a multi-level unsupervised community-detection algorithm (Louvain) was used to group commonly co-reported adverse drug reactions, thus defining syndrome-like frameworks [27].

Results

Characteristics of patients in the French PH Registry

From 1 January 2007 to 31 December 2022, 10 precapillary PH patients exposed to gemcitabine were identified. After review of patient records, one patient was excluded because of PH associated with severe chronic lung disease and was classified as Group 3 PH (PH associated with lung diseases and/or hypoxia). Finally, nine cases were retained for the diagnosis of gemcitabine-associated PH or aggravation of PH following exposure to gemcitabine (table 1). One of the patients in our series has already been published as a case report by Turco *et al.* [21]. One patient with previously diagnosed PVOD presented with clinical and haemodynamic worsening following exposure to gemcitabine. All patients are male, with a median age at diagnosis of 78 (58–83) years. Seven patients were former smokers (mean 48 pack-years), and two were never-smokers. None of the patients had been exposed to organic solvents or drugs known or suspected of inducing PAH. Mild to moderate COPD has been reported in five patients and one patient had diffuse ILD (predominantly subpleural reticulation) with no functional respiratory impairment prior to exposure to gemcitabine.

Gemcitabine exposure

The indications for gemcitabine included pancreatic adenocarcinoma (n=2), urothelial carcinoma (n=2) and nonsmall cell lung cancer (n=5) (table 1). Gemcitabine was administered as monotherapy in four patients or in combination with mainly platinum salts (three patients received carboplatin, two cisplatin). Two patients had undergone lobectomy. No patients underwent thoracic radiotherapy. The median time from initiation of gemcitabine to first symptoms was 6 (1–49) months. The median delay from first and last gemcitabine injection to diagnosis of PAH was 7 (4–50) and 0.5 (0.25–16) months, respectively. The median number of total chemotherapy injections was 16 (6–24), with a usual gemcitabine dose of 1000 $mg \cdot m^{-2}$. At the time of PH diagnosis, five patients (55%) had a partial response to treatment or were in remission, three patient (33%) had tumour progression and one patient (11%) had stable neoplastic disease.

TABLE 1 Patient characteristics at diagnosis or aggravation of pulmonary hypertension

Age years	78 (58–83)
Sex, male/female	9/0
Smoking exposure	
Never-smoker	2
Active smoker	0
Former smoker (weaned >10 years)	7
Exposure to organic solvents	0
Gemcitabine	
Number of gemcitabine injections	16 (6–24)
Time from first gemcitabine injection to diagnosis of PAH, months	7 (4–50)
Time from last gemcitabine injection to diagnosis of PAH, months	0.5 (0.25–48)
Indication for gemcitabine	
Pancreatic cancer	2
Lung cancer	5
Bladder and urinary tract cancer	2
Chemotherapy regimen	
Gemcitabine + carboplatin	3
Gemcitabine + cisplatin	2
Gemcitabine	4
Cancer status at diagnosis of PAH	
Remission or partial response	5
Stable	1
Progression	3
Relapse	0
Other risk factors	
COPD	5
ILD	1

Data are presented as median (range) and n. PAH: pulmonary arterial hypertension; ILD: interstitial lung disease.

PH assessment at diagnosis

All the patients with gemcitabine-associated PH had rapidly progressive dyspnoea; seven were in NYHA functional class III and two in NYHA functional class IV at diagnosis (table 2). The median FEV_1 and TLC values were 68% (52–99) and 89% (64–112) of the predicted values, respectively. D_{LCO} was reduced in all patients, with a median D_{LCO} of 30% (14–37%) of the predicted value. Hypoxaemia was observed in all patients with a median P_{aO_2} of 55 (48–73) mmHg. All patients had increased plasma BNP or NT-proBNP levels at diagnosis. According to the European Society of Cardiology (ESC)/European Respiratory Society (ERS) three-strata model [28], five patients were in the high-risk population for mortality, and four patients were at intermediate risk [29] (table 2). Four patients had CT features suggestive of PVOD including reticulations (n=4), ground-glass opacities (n=1) and mediastinal adenopathy (n=2). Three patients had moderate diffuse emphysema and one patient had minimal emphysema [30]. No patient had evidence of thromboembolic disease or tumour embolism on CT and ventilation/perfusion lung scans. RHC showed severe precapillary PH with a median mPAP of 40 (26–47) mmHg, PAWP of 8 (7–14) mmHg, RAP of 7 (4–19) mmHg, cardiac index of 2.4 (1.6–3.9) $L{\cdot}min^{-1}{\cdot}m^{-2}$ and PVR of 6.3 (3.1–12.6) Wood units (table 2). An acute vasodilator test was performed in four patients, all of whom tested negative, thereby confirming the absence of a post-capillary PH component.

Follow-up and outcomes

After diagnosis of PH, gemcitabine was discontinued for all patients. Three patients showed spontaneous clinical improvement after discontinuation of gemcitabine alone, and two were still alive without having received PAH-approved drugs. Monotherapy with PAH-approved drugs was administered to five patients, including a phosphodiesterase type 5 (PDE5i) inhibitor in four and an endothelin receptor antagonist in one. Combination therapy was not administered to any patient. Two patients experienced clinical improvement or stabilisation, while three had worsening PH. After the introduction of PDE5i, the respiratory status of two patients deteriorated to hypoxic respiratory failure associated with signs of right heart failure. After a median follow-up of 18 (1–59) months, five patients (55%) died. The cause of death among these patients was diverse: acute right heart failure was the cause in two cases, tumour progression was the cause in two others, while the cause remained undetermined in the last case. The patient with pre-existing PVOD deteriorated progressively after exposure to gemcitabine. Of the patients who improved after gemcitabine discontinuation, two had features of PVOD on chest CT.

TABLE 2 Clinical, biological, functional, haemodynamic and radiological features at diagnosis or aggravation of pulmonary hypertension

NYHA functional class	
III	7
IV	2
BNP or NT-ProBNP	
Low risk	0
Intermediate risk	4
High risk	5
Arterial blood gases in ambient air	
P_{aO_2} mmHg	55 (48–73)
P_{aCO_2} mmHg	32 (29–42)
Pulmonary function test	
FEV_1 % pred	68 (52–99)
TLC % pred	89 (64–112)
D_{LCO} % pred	30 (14–37)
Transthoracic cardiac ultrasound (n=6)	
sPAP mmHg	60 (43–90)
Haemodynamic parameters, RHC (n=9)	
mPAP mmHg	40 (26–47)
PAWP mmHg	8 (7–14)
RAP mmHg	7 (4–19)
CO $L{\cdot}min^{-1}$	4.5 (3.1–7.9)
Cardiac index $L{\cdot}min^{-1}{\cdot}m^{-2}$	2.4 (1.6–3.9)
PVR Wood units	6.3 (3.1–12.6)
Acute vasodilator response (n=4)	0
High-resolution CT scan	
Emphysema	4
Interlobar septal line	4
Centrilobular fuzzy nodule	1
Mediastinal opacity	0
Mediastinal adenopathy	2
Pleural effusion	4
Pericardial effusion	0

Data are presented as median (range) and n. Multiparametric prognostic risk assessment: low risk (brain natriuretic peptide (BNP) <50 $ng{\cdot}L^{-1}$ or N-terminal pro-BNP (NT-proBNP) <300 $ng{\cdot}L^{-1}$), intermediate risk (BNP 50–300 $ng{\cdot}L^{-1}$ or NT-proBNP 300–1400 $ng{\cdot}L^{-1}$) and high risk (BNP >300 $ng{\cdot}L^{-1}$ or NT-proBNP >1400 $ng{\cdot}L^{-1}$). NYHA FC: New York Heart Association Functional Class; % pred: percentage of predicted value; P_{aO_2}: partial pressure of oxygen in arterial blood; P_{aCO_2}: partial pressure of carbon dioxide in arterial blood; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; D_{LCO}: carbon monoxide diffusion capacity corrected by haemoglobin concentration; RHC: right heart catheterisation; sPAP: systolic pulmonary arterial pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary artery wedge pressure; RAP: right atrial pressure; CO: cardiac output; PVR: pulmonary vascular resistance; CT: computed tomography.

The overall survival from the diagnosis of gemcitabine-associated PH is shown in figure 1. The median overall survival was 18 months, and the survival rates at 12 and 24 months were 77% and 44%, respectively.

Results of pharmacovigilance disproportionality analysis in the WHO pharmacovigilance database

On June 2023, we identified 109 cases reporting at least one adverse event related to PH with gemcitabine in the WHO pharmacovigilance database. PH was reported in 51 cases, right ventricular failure in 21 cases, tricuspid valve incompetence in 17 cases, PAH in 10 cases, cor pulmonale in six cases, and pulmonary valve incompetence, pulmonary artery dilatation and right ventricular dysfunction in two cases. Moreover, one case with each of the following symptoms was identified: PVOD, increased pulmonary arterial pressure, right ventricular hypertrophy, right ventricular enlargement, abnormal pulmonary arterial pressure, increased right ventricular systolic pressure, pulmonary hypertensive crisis and decreased right ventricular ejection fraction. Most frequently associated symptoms were dyspnoea (n=28), pleural effusion (n=15), cardiac failure (n=14), mitral valve incompetence (n=14), anaemia (n=12), pericardial effusion (n=12) and congestive cardiac failure (n=11). Furthermore, most frequently associated drugs to gemcitabine were paclitaxel (n=13), cisplatin (n=9), carboplatin (n=9), bevacizumab (n=6) and oxaliplatin (n=6). Gemcitabine was the only suspected antineoplastic drug in 55 cases, of which interferon β and methamphetamine were co-suspected in one case each.

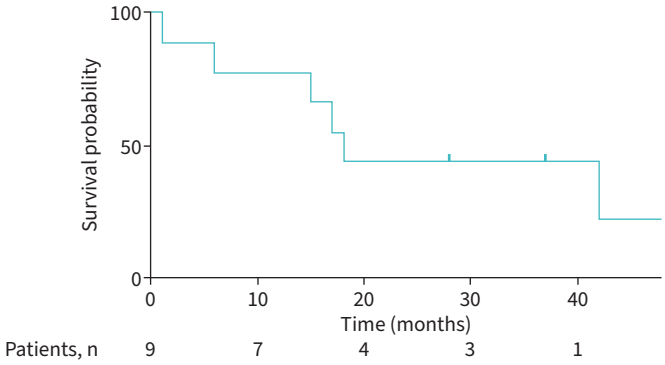

FIGURE 1 Overall survival from diagnosis of pulmonary hypertension after exposure to gemcitabine. Patients who were censored are represented by a vertical line.

Most cases originated from the USA (65.1%), France (13.8%) and Germany (10.1%); 54.1% of reports concerned females, and the mean±SD age was 62.8±14.2 years. Gemcitabine dose ranged from 500 to 2000 $mg \cdot m^{-2}$ per cycle with a median dose of 1000 $mg \cdot m^{-2}$, and median (IQR) time to onset was 2.5 (1.3–4.8) months. When gemcitabine was stopped (available data for 22 cases), symptoms improved in 12 cases and did not in 10 cases. In one case of right ventricular failure gemcitabine was reintroduced with reappearance of symptoms. In eight cases (two PH, one PAH, two tricuspid valve incompetence, two right ventricular failure and one cor pulmonale) the reporter assessed the causal link with gemcitabine exposure using the WHO causality assessment method or by expert judgement. The role of gemcitabine was considered probable in one case, possible in four and unlikely in three.

The disproportionality signal for all adverse events included in the SMQ PH was significant (IC=0.88; 95% CI 0.59–1.14). Higher and significant disproportionality signals were found for PH (IC=0.67; 95% CI 0.24–1.04), right ventricular failure (IC=1.14; 95% CI 0.46–1.69), tricuspid valve incompetence (IC=0.96; 95% CI 0.20–1.57) and cor pulmonale (IC=2.02; 95% CI 0.65–2.95). Using the network analysis and the multi-level community-detection algorithm we identified 21 clusters grouping 62 co-reported adverse events. All clustered networks containing respiratory adverse events are presented in figure 2. Cases of cor

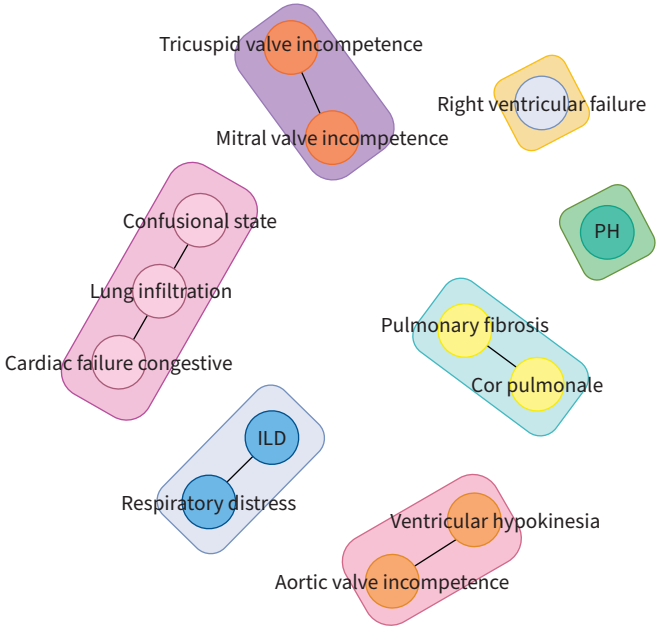

FIGURE 2 Network clusters of co-reported cardiopulmonary adverse events with gemcitabine. PH: pulmonary hypertension; ILD: interstitial lung disease.

pulmonale are often associated with pulmonary fibrosis; cases of respiratory distress with interstitial disease and tricuspid and valve incompetence are often reporded together. Moreover, a cluster of cardiac failure congestive and lung infiltration was identified. However, PH and right ventricular failure with gemcitabine are not co-reported with other adverse events.

Discussion

The cases reported in this study represent, to our knowledge, the only descriptive case series of patients with gemcitabine-associated PH in a large pharmacovigilance database. From the WHO pharmacovigilance database, we found a significant signal with 109 cases of PH or associated symptoms reported with gemcitabine. Gemcitabine was the only suspect drug in most of the cases. Most of the PH cases were not associated with other cardiovascular adverse events. No specific signal of PAH was found using other antineoplastics as control group, although the proportion of PAH coded as PH is unknown. From data recorded in the French PH Registry, we identified nine cases of PAH induced by gemcitabine including one case of PAH worsened by gemcitabine. Six patients experienced clinical improvement or stabilisation in NYHA functional class following the discontinuation of gemcitabine, with some probably benefiting from the addition of PAH-approved medications. There is a real complementarity between the study based on all the cases reported in Vigibase® and the more detailed data from the French pharmacovigilance network.

Gemcitabine is a pyrimidine antimetabolite that must undergo several phosphorylations by intracellular kinases to form the active di- and triphosphate compounds [1]. It induces cell death in the S-phase in a dose- and time-dependent manner. Several studies have shown that gemcitabine pulmonary toxicity can lead to acute and fatal respiratory failure [4–6]. Pulmonary toxicity associated with gemcitabine can be expressed in a variety of ways and can be retrieved in the Pneumotox® database, such as acute non-cardiogenic pulmonary oedema, hypersensitivity pneumonitis (including acute respiratory distress syndrome), acute ILD or pulmonary fibrosis [8–10, 31]. Multiple gemcitabine-related toxicities, including capillary leak syndrome [20] and direct cytokine-mediated toxicity, may contribute to gemcitabine-associated PH. Only four cases of PAH have been so far published in the literature, including two cases of PVOD (table 3). In 2019, Shen *et al.* [19] reported a case of gemcitabine-induced PAH in which the patient presented with PAH following a course of gemcitabine for metastatic cholangiocarcinoma. The diagnosis was suggested by transthoracic echocardiography (TTE) in view of suggestive clinical features. A study by Vansteenskiste *et al.* [22] described a patient treated for metastatic lung cancer receiving third-line chemotherapy with gemcitabine. The clinical, radiological and haemodynamic signs (mPAP 35 mmHg, PAWP 7 mmHg) were in favour of PVOD after two cycles of gemcitabine, and the diagnosis was confirmed by autopsy. Recently, Hlavaty *et al.* [23] evaluated all reported cases of PH from the WHO pharmacovigilance database using the Bayesian neural network method. Several chemotherapies were identified, including gemcitabine, supporting the data from our study.

In recent years, a multitude of clinical studies, case series and published case reports have shown that thrombotic and vascular events appear to be more frequent during treatment with this agent [7]. Gemcitabine may also be able to activate the coagulation cascade, possibly inducing endothelial damage that may be responsible for thrombotic microangiopathy [7, 32]. In an animal study performed *ex vivo* to assess the acute and delayed toxicities of gemcitabine in isolated pig lung, the drug was found to induce vasoconstriction of the pulmonary capillaries, leading to an increase in mPAP [33].

There are clinical and paraclinical similarities between the reported case of gemcitabine-associated PVOD and patients from our study. Four patients had CT findings suggestive of PVOD (reticulations, ground-glass opacities and mediastinal adenopathy) associated with profound hypoxaemia and a decrease in D_{LCO}. In addition, the respiratory status of three patients worsened with acute respiratory failure after introduction of PDE5i. Obtaining a differential diagnosis between PAH and PVOD is challenging. These two conditions have similar clinical and haemodynamic characteristics, but can be distinguished by their physiopathology and prognosis [34]. In 2015, Ranchoux *et al.* [35] reported an association between PVOD and chemotherapy, based on an analysis of French cases and a literature review. Alkylating agents, primarily cyclophosphamide (43.2%), were the class most frequently reported in association with PVOD (83.8% of cases). In addition, the French PH network recently reported cases of PVOD in patients exposed to mitomycin-C (MMC) [18, 36].

In this cohort, we observed a significant male predominance (ratio 9:0). This is probably explained by the type of cancer, since the majority of patients had lung cancer induced by smoking. However, a predominance of males is observed in sporadic PVOD cases among non-mutation carriers, a pattern that differs from PAH [37, 38]. None of the patients from our cohort were genetically tested for mutations in PAH/PVOD predisposing genes. It is important to note that platinum salts and gemcitabine were

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TABLE 3 Case reports of pulmonary arterial hypertension (PAH) associated with gemcitabine in the literature

First author [ref.]	Sex/age (years)	Indication of gemcitabine	Diagnosis	Time to occurrence of PAH from introduction of gemcitabine	Naranjo's score	Previous chemotherapy	Diagnostic examination	Treatment and follow-up
Vansteenskiste [22]	M/57	Lung adenocarcinoma (cT4N0M0)	PVOD	2 months (2 cycles)	9	1st line: 5 cycles of docetaxel and 4 cycles of cisplatin 2nd line: 6 cycles of docetaxel and cisplatin 3rd line: 2 cycles of mitomycin C + vindesine Then 2 cycles of gemcitabine	RHC (mPAP 35 mmHg, PAWP 5 mmHg)	Death PVOD confirmation at autopsy
Casadei Gardini [20]	F/65	Pancreatic ductal carcinoma (pT3N0M0, pancreatectomy then adjuvant chemotherapy)	PH and capillary leak syndrome	7 months +7 days	6	No	TTE (sPAP 58 mmHg)	Improvement after cessation of gemcitabine
Turco [21] (included in our study)	M/83	Pancreatic adenocarcinoma	PVOD	7 months (8 cycles)	7	No	RHC (mPAP 45 mmHg, PAWP 7 mmHg, cardiac index 2.7 $L \cdot min^{-1} \cdot mL^{-1}$)	Improvement after cessation of gemcitabine
Shen [19]	M/82	Metastatic cholangiocarcinoma (liver and lung)	PAH	1 month (during the 2nd cycle)	6	No	TTE (sPAP 35 mmHg)	Death

F: female; M: male; PVOD: pulmonary veno-occlusive disease; RHC: right heart catheterisation; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary artery wedge pressure; PH: pulmonary hypertension; TTE: transthoracic cardiac ultrasound; sPAP: systolic pulmonary arterial pressure assessed by cardiac ultrasound.

co-administered in five out of nine patients, which may contribute to the development of PAH/PVOD. The role of platinum salts in the development of PAH or PVOD has not yet been clearly described to our knowledge, but it is important to consider a potential additive effect of various chemotherapy agents [7, 39]. An additive effect of multiple chemotherapeutic agents in the development of PH cannot be ruled out [35]. The presence of an underlying respiratory disease in six of the patients may have contributed to the genesis of PH, playing the role of a "second hit" on pulmonary vascular remodelling. This hypothesis has been observed in individuals with a genetic predisposition (such as a *BMPR2* mutation) following amphetamines or anorexigen exposure [40]. Exposure to gemcitabine may have increased PVR in these patients. This implies clinical and ultrasound monitoring if there is a pre-existing risk factor for PH.

The notable clinical and haemodynamic improvement observed after the discontinuation of gemcitabine strongly suggests the role of this drug in the onset of PH. Data from the WHO pharmacovigilance database indicate that symptoms improved in 12 out of 22 cases where gemcitabine was discontinued. Similarly, from the French PH Registry, four out of our nine patients improved upon cessation of chemotherapy. This kind of reversibility is comparable to that observed in patients with dasatinib-associated PAH, a tyrosine kinase inhibitor indicated for the treatment of chronic myeloid leukaemia [41, 42]. PVOD after treatment with MMC is rare but associated with a poor prognosis. The median overall survival in the Certain *et al.* [37] study was 20 months, and the survival rates at 12 and 24 months were 58% and 18%, respectively. These results highlight a poorer prognosis for MMC-induced PH without any reversibility compared with gemcitabine.

Disproportionality studies using the WHO pharmacovigilance database suffer from several limitations. Individual Case Safety Reports in the WHO pharmacovigilance database are spontaneously reported by health professionals and patients in 134 countries worldwide. However, this system for detecting safety signals grapples with challenges such as the heterogeneity of reported cases, variations in regional drug use, and difference in pharmacovigilance systems. Moreover, selective reporting of adverse reactions, coupled with a lack of comprehensive clinical data to confirm the validity of these reactions (including RHC for PH), could introduce numerous biases. Nevertheless, these data have been consolidated by a very thorough clinical analysis of cases from the French pharmacovigilance network.

Nevertheless, as highlighted by Hlavaty *et al.* [23] combining data with PAH registries and pharmacovigilance databases or epidemiological studies represents a promising approach for revealing associations between PAH and certain drugs, thereby predicting potential pulmonary vascular toxicities. The nine cases reported in this study come from national databases that have been collecting data since gemcitabine received marketing authorisation. This ensures that the data are not influenced by biases related to specific centres or temporal variations. However, it is important to note that our study cannot definitively ascertain the actual incidence of gemcitabine-associated PAH or PVOD in cancer patients, which may be underestimated due to the potential absence of referral for patients with advanced neoplastic diseases and the possible misdiagnosis.

In conclusion, our study underscores the potential association between gemcitabine exposure and PAH/PVOD, while acknowledging that the pathophysiological mechanisms are not yet entirely understood. The study also points out the possible reversibility of PH following the discontinuation of gemcitabine. It is thus crucial to inform physicians, urging them to remain vigilant for symptoms like dyspnoea following the administration of this type of chemotherapy. They should consider the possibility of PH in patients treated with gemcitabine who experienced dyspnoea and propose early detection by TTE. Given the information gathered here and in the scientific literature, gemcitabine chemotherapy could be added to the list of drug treatments potentially linked to the onset of PH, thereby heightening vigilance during its usage. Further clinical and preclinical studies are needed to understand the pathophysiological mechanisms involved. It would be interesting to obtain histological evidence of gemcitabine-induced PH to better characterise the associated pulmonary vascular lesions.

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Ethics statement: The registry was established in accordance with French bioethics laws (Commission Nationale de l'Informatique et des Libertés (842063)) and all patients gave their informed consent to participate in this registry. The protocol of the disproportionality analysis was pre-registered on Open Science Framework (https://osf.io/9rt5s/) and reported according to READUS-PV (https://readus-statement.org/).

Conflict of interest: X. Jais reports grants or contracts from Acceleron, Janssen, MSD and Bayer HealthCare, outside the submitted work; and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Janssen and MSD, outside the submitted work. L. Savale reports grants or contracts from Bayer, Janssen and Merck, outside the submitted work; and speaker fees from Janssen, outside the submitted work. O. Sitbon reports grants or contracts from Acceleron, AOP Orphan, Janssen, GSK and MSD, outside the submitted work; consulting fees from Altavant, Gossamer Bio, Janssen and MSD, outside the submitted work; payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing or educational events for AOP Orphan, Janssen, Ferrer and MSD, outside the submitted work; and participation on a Data Safety Monitoring Board or Advisory Board for Acceleron, Altavant, Gossamer Bio, Janssen, MSD and Ferrer, outside the submitted work. M. Humbert reports grants or contracts from Acceleron, AOP Orphan, Janssen, Merck and Shou Ti, outside the submitted work; consulting fees from Acceleron, Aerovate, Altavant, AOP Orphan, Bayer, Chiesi, Ferrer, Janssen, Merck, MorphogenIX, Shou Ti, Tiakis and United Therapeutics, outside the submitted work; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events for Janssen and Merck, outside the submitted work; and participation on a Data Safety Monitoring Board or Advisory Board for Acceleron, Altavant, Janssen, Merck and United Therapeutics, outside the submitted work. P. Bonniaud reports a research grant from AstraZeneca, outside the submitted work; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Sanofi and AstraZeneca, outside the submitted work; support for attending medical and research meetings from AstraZeneca, Novartis, Sanofi, Roche and Boehringer, outside the submitted work; and personal fees for advisory boards from AstraZeneca, Novartis, Sanofi, GSK, Roche and Boehringer, outside the submitted work. D. Montani reports grants or contracts from Acceleron, Janssen and Merck MSD, outside the submitted work; consulting fees from Acceleron, Merck MSD, Janssen and Ferrer, outside the submitted work; and speaker fees from Bayer, Janssen, Boehringer, Chiesi, GSK, Ferrer and Merck MSD, outside the submitted work. The remaining authors have nothing to disclose.

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