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Gemcitabine-Related Pneumonitis in Pancreas Adenocarcinoma—An Infrequent Event: Elucidation of Risk Factors and Management Implications

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Abstract

A total of 2440 pancreatic cancer patients who received gemcitabine treatment were screened for gemcitabine-related pneumonitis (GRP). The observed rate of GRP was 1.1%. History of smoking, alcohol use, and history of underlying lung disease were identified as possible risk factors of GRP. Early pulmonary consult and cessation of gemcitabine is recommended once clinical suspicion arises.

Background—Gemcitabine-related pneumonitis (GRP) has been reported relatively frequently for pancreas cancer in the literature; however, underlying risk factors and optimal management remain to be defined. We studied a cohort of patients with GRP and investigated potential predisposing factors in pancreatic cancer patients.

Patients and Methods—A total 2440 patients at Memorial Sloan Kettering Cancer Center were identified between January 1, 2000, and December 31, 2012, and were screened for grade 2 or higher GRP in an institutional tumor registry and using an ICD billing code database. Demographic and clinical information was extracted by electronic chart review.

Results—A total of 28 patients (1.1%) with GRP were identified. Incidence of grade 2, 3, and 4 reactions were 7 (25%), 18 (64%), and 3 (11%), respectively. No GRP-related mortality was observed. Twenty-one patients (75%) reported a history of cigarette smoking. Seventeen patients (61%) were alcohol users. Six patients (21%) were either regular or heavy drinkers. Most patients (93%) had either locally advanced or metastatic disease. Three patients (11%) underwent a diagnostic bronchoscopy, and in 1 patient a diagnosis of organizing pneumonia was established. Morbidity was significant; 3 patients (11%) required treatment in the intensive care unit. All hospitalized patients received steroid treatment.

Conclusion—GRP is relatively uncommon but incurs significant morbidity. Potential risk factors include advanced-stage disease, along with smoking and alcohol consumption and possibly

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Disclosure

The authors have stated that they have no conflicts of interest.

underlying lung disease. We recommend a high level of clinical alertness regarding the diagnosis, early pulmonary referral, and cessation of gemcitabine on suspicion of GRP.

Keywords

Adenocarcinoma; Capecitabine; Erlotinib; Gemcitabine; Nab-paclitaxel; Oxaliplatin; Pancreas; Pneumonitis

Pancreatic cancer is one of the most challenging human malignancies and ranks as the fourth leading cause of cancer-related mortality in the United States, with a projection that it will be second only to non–small-cell lung cancer by 2030.[1,2] Five-year survival expectation remains poor, and most patients present with locoregionally advanced and/or metastatic disease where treatment goals are noncurative in intent. Several risk factors for pancreas adenocarcinoma have been identified, including a history of long-standing diabetes, cigarette smoking, chronic and hereditary pancreatitis, and several genetic predisposition syndromes.[3–6] Although much work is underway evaluating novel targeted therapies and other agents in pancreas adenocarcinoma, cytotoxic systemic therapy, particularly gemcitabine, remains a mainstay of treatment in all stages of pancreas adenocarcinoma.

Gemcitabine has been shown to have efficacy as a single agent and in combination with other chemotherapeutic agents.[7,8] In particular, a recent phase 3 trial (MPACT) evaluated the addition of nab-paclitaxel combined with gemcitabine and demonstrated an improvement in overall survival, tumor response, and progression-free survival compared to single-agent gemcitabine.[9] Toxicities for gemcitabine include nausea, vomiting, dyspnea, myeleosuppression, elevated liver enzymes including bilirubin levels, rash, diarrhea, and, less often, capillary leak syndrome and pneumonitis.[10–12] Gemcitabine-related pneumonitis (GRP) has been documented in patients with varied cancers in sites such as lung, ovary, breast, gallbladder, and pancreas[13–19] and is a potentially fatal complication that may incur significant morbidity and, rarely, mortality.[19–21] The incidence of GRP has been reported in different pooled studies of various cancers at rates ranging from 0.02% to 0.27%.[22,23] Several clinical trials report a higher rate of pneumonitis in treatment that combines gemcitabine with other agents such as nab-paclitaxel and erlotinib.[9,24] The clinical presentation of drug-related pneumonitis is composed of nonspecific symptoms such as cough, dyspnea, fever, and hypoxemia, along with the potential for major pulmonary compromise.[25,26] Therefore, like other drug-related pneumonitis etiologies, GRP is a diagnosis of exclusion and is defined as interstitial infiltration of lung parenchyma with typical radiographic findings such as diffuse or patchy ground-glass or reticular opacities in the absence of other etiologic factors such as infectious or autoimmune processes.[26,27]

The underlying pathogenesis of GRP remains unclear. One study suggests that increased expression of pro-inflammatory cytokines promotes lung toxicity in the setting of thoracic radiation in animal models.[28] Another study demonstrated an increased level of KL-9, a high-molecular-weight glycoprotein commonly observed in drug-induced pneumonitis.[29] However, this is a nonspecific marker that has been shown to be increased in other types of interstitial lung diseases as well.[30] On the other hand, various case reports have also demonstrated eosinophilic infiltration of lung parenchyma after gemcitabine therapy in the

setting of various cancer treatments, suggesting a hypersensitivity reaction.[13,21,27] More experimental studies are required to ascertain the underlying pathogenesis of GRP.

Although no standard treatment has been established for druginduced pneumonitis, a first step is discontinuation of the offending agent. Available evidence also suggests benefit of glucocorticoid therapy.[31] Additional supportive care is also recommended with supplemental oxygen, bronchodilators in the presence of bronchospasm, and mechanical ventilation as clinically needed.[32]

Given the many uncertainties regarding the background and risk factors for GRP, we evaluated the incidence and clinical factors, as well as the identification of potential risk factors, of GRP in patients with pancreas adenocarcinoma receiving gemcitabine or gemcitabine-based therapy.

Patients and Methods

Study Population

We retrospectively queried the Memorial Sloan Kettering Cancer Center institutional tumor registry and ICD billing code database for pancreatic cancer patients who developed “pneumonia” or “lung-related” events while receiving gemcitabine-based treatment in a 12-year period commencing January 1, 2000, and ending December 31, 2012. A total of 2440 pancreatic cancer patients were identified as having received gemcitabine therapy, and of those, 173 patients were identified as having nonspecific “pneumonia” during gemcitabine treatment (Figure 1). Patients with a grade 2 or higher event were included in our analysis. Specifically we opted to exclude patients with grade 1 symptoms, given the great difficulty in ascertaining their association with gemcitabine. After a detailed chart review of these patients, 28 patients were identified as having pneumonitis attributed to gemcitabine treatment and were included in our study on the basis of the definition stated below. All patients had either cytologically or pathologically confirmed diagnosis of pancreatic adenocarcinoma. The study was reviewed by the Memorial Sloan Kettering Cancer Center institutional review and privacy board.

Data Collection and Statistical Analysis

Demographic and clinical information was abstracted from electronic medical records using the chart review method by trained medical personnel. Gemcitabine-associated pneumonitis was defined as an interstitial inflammation of lung parenchyma in the absence of an infectious etiology with typical ground-glass and reticular opacities on radiographic imaging and response to steroid treatment. Pulmonary consultant notes and corresponding imaging were reviewed for patients who were deemed to be eligible. Grading of pneumonitis was stratified on the basis of Common Terminology Criteria for Adverse Events version 4.03 guidelines by the National Cancer Institute, and a grade 2 reaction was considered as symptomatic without interfering with adult daily living. A grade 3 reaction included symptoms that interfered with activities of daily living (typically implying hospitalization), and a grade 4 reaction was determined as a life-threatening reaction, typically requiring treatment in the intensive care unit and ventilation support. Body mass index was classified

as normal (18–25 kg/m^2), overweight (25–30 kg/m^2), or obese (> 30 kg/m^2). Clinical history, including medical and surgical history, social history including alcohol and smoking history, allergy history, disease status at the time of pneumonitis, treatment history along with dose of gemcitabine treatment, and grade of pneumonitis, were obtained from detailed chart medical record review. Demographic information, including age, gender, and race, were retrieved. Repeat chart review was performed to verify the accuracy of the collected clinical and demographic information. Descriptive statistical reporting was performed by trained personnel.

Results

A total of 28 (1.1%) of 2440 patients were identified to have developed grade 2 or higher grade GRP between January 1, 2000, and December 31, 2012. The median age of the 28 patients was 69 years, and 18 patients (64%) were older than 60. Of these 28 patients, 15 (54%) were female and 13 (46%) were male (Table 1). Twenty-seven patients (96%) were white and 1 (4%) patient was Asian. Fifteen patients (54%) were identified to be overweight, and 5 patients (18%) were obese. Four patients (14%) reported a history of chronic obstructive pulmonary disease, and 2 patients (7%) had a history of prior interstitial lung disease (Table 2). Both patients were diagnosed with idiopathic pulmonary fibrosis, and 1 patient required home oxygen (Table 1). Thoracic radiation had been administered to 1 patient to treat Hodgkin lymphoma.

Twenty-one patients (75%) had an adenocarcinoma of the head of the pancreas; the remaining 25% of patients had a tumor in either the pancreas body or tail. Twenty patients (71%) had metastatic disease at the time of development of GRP. Of these, 7 (35%) were identified to have metastatic disease to lungs, either alone or along with liver metastases and peritoneal carcinomatosis. Six patients (21%) had either locally recurrent or locally advanced disease at the time of GRP. Only 2 patients (7%) had pneumonitis in the setting of adjuvant treatment. Of these 28 GRP patients, 20 patients (71%) were receiving single-agent gemcitabine, and 8 patients (29%) were receiving combination treatment with other agents, including erlotinib (n = 3), oxaliplatin (n = 2), and capecitabine (n = 3), at the time of GRP diagnosis (Table 3). Patients received gemcitabine treatment in a dose range of 1000 to 600 mg/m^2. Complete treatment details are summarized in Table 3.

Seven patients (25%) developed a grade 2 GRP reaction, while 18 patients (4%) had a grade 3 reaction. Three patients (11%) had a grade 4 reaction that required treatment in intensive care. No GRP-related mortality was identified. Twenty-one patients (75%) required hospitalization, and 3 patients were managed in intensive care unit. Three patients underwent a diagnostic bronchoscopy. In 1 patient, organizing pneumonia, which is a rare presentation of drug-induced pneumonitis,[21] was identified. In the other 2 patients, nonspecific inflammatory cells were identified. No organism grew in specimen cultures. All patients who required hospitalization received steroid medication with supportive treatment after ruling out an infectious etiology or were empirically treated on the basis of clinical presentation and radiologic findings. The remainder of the patients (25%) were treated by discontinuing gemcitabine with symptomatically directed management in an outpatient setting.

Twenty-one patients (75%) reported a history of smoking cigarettes, and of these, only 1 patient (4%) was an active smoker after the diagnosis of malignancy. Eight (40%) of 20 former smokers had discontinued cigarette smoking after their diagnosis of pancreas adenocarcinoma and were not actively smoking cigarettes within the previous year. In addition, 1 patient reported a significant history of secondhand cigarette smoke. Of these smokers, 19 (90%) smoked more than 20 pack-years, and 1 patient had a 10 pack-year history. For 1 patient, we could not quantify the amount of cigarette smoking. Seventeen patients (61%) had a history of alcohol consumption, and of these, 11 patients (65%) reported consuming an occasional drink, while 6 patients (35%) reported daily to regular or heavy to binge drinking. Nine patients (32%) had a history of allergies; of these, 4 were allergic to penicillin or cephalosporin.

Discussion

In our study, we identified an incidence of GRP as 1.1% in a population of 2440 patients with pancreas adenocarcinoma treated with gemcitabine or gemcitabine-based therapy over a 12-year period. No mortality was observed in our patient population. However, 21 patients (75%) had significant morbidity, and 3 patients had grade 4 pneumonitis events requiring intensive medical management. We observed a high smoking rate (75%) along with a history of significant alcohol consumption (35%), and the majority of patients had advanced-stage disease at the time of GRP.

The incidence rate that we observed was higher than in previous studies.[23,24] Moreover, if patients who received gemcitabine treatment at local oncology clinics were also included, the true incidence rate might have been even higher than our observed rate of 1.1%. The difference in incidence rate between our study and the aforementioned studies could be explained by increased awareness and early recognition of GRP in patients with pancreas cancer receiving gemcitabine therapy who develop respiratory symptoms while receiving treatment. Risk factor identification indicated that the majority of the GRP patients were former or recent cigarette smokers, even though a majority were not active smokers at the time of occurrence of GRP. A significant alcohol history was notable in our patient population. Additionally, a majority of the patients had locally advanced and advanced-stage metastatic disease at the time of GRP.

Our findings suggest that a history of underlying lung disease, cigarette smoking, and alcohol history along with advanced-stage cancer may be potential risk factors for GRP in pancreatic cancer patients. Although our study is limited with regard to an ability to assess the impact of other chemotherapeutic agents in combination with gemcitabine, a phase 3 study by Von Hoff et al[9] reported significantly increased pneumonitis rates with the combination of gemcitabine and nab-paclitaxel compared to gemcitabine alone (4% vs. 1%, respectively). These data consolidate the necessity of a high level of awareness for emerging respiratory symptoms for early intervention and management of a potential diagnosis of GRP, particularly in the setting of combined therapy (eg, gemcitabine and nab-paclitaxel therapy, which is now a commonly used first-line standard therapy for patients with newly diagnosed untreated pancreas adenocarcinoma).

Our data suggest a lack of a clear temporal relationship between gemcitabine administration and GRP. Eighteen (64%) of 28 patients developed GRP after administration of at least 10 doses of gemcitabine, suggesting that there is a tendency to develop reactions after cumulative doses. However, we also observed reactions after very limited exposure to gemcitabine, such as after a first dose (Table 3), indicating that GRP might be evolving on the basis of diverse pathophysiologic mechanisms, including hypersensitivity reactions.

Several reports in the literature describe GRP in pancreatic cancer patients (Table 4). A case report described a 76-year-old man with GRP after a ninth dose of adjuvant single-agent gemcitabine treatment. Diffuse ground-glass opacities were observed on computed tomographic (CT) scan, and the patient was successfully treated with steroids and supportive therapy.[33] No background information regarding social history was reported in this case. Another case report described a patient with a 50 pack-year cigarette smoking history who developed GRP after a fifth cycle of adjuvant gemcitabine treatment.[13] This patient was also observed to have diffuse bilateral ground-glass lung appearance and was managed by high-dose steroid therapy, broad-spectrum antibiotics, and supportive oxygen treatment without mechanical ventilation requirement. A 68-year-old man with 75 pack-year smoking history was reported in a case study with GRP after receiving his second dose of gemcitabine.[22] The patient was found to have bilateral ground-glass opacities and was initially managed by only oxygen treatment with no significant response, then subsequently managed by steroids with significant clinical improvement. Similar case reports are summarized in Table 4.[15,34,35] A report of 9 GRP cohort cases suggested similar imaging findings as described above, and all patients in the study received steroid treatment along with supportive therapy.[25] However, strikingly, the disease of 2 patients did not respond to steroid treatment, and they died of progressive respiratory failure. All these studies suggest that GRP is a potentially fatal complication and that steroid management should be initiated promptly, perhaps even in severe cases while ruling out infectious etiologies in suspected patients along with supportive treatment.

Extensive evidence suggests that cigarette smoking plays a significant role in occurrence of acute lung injury and increases the risk of adult respiratory distress syndrome and other lung diseases.[30,36–38] The studies suggest that bronchoalveolar damage, which is executed particularly by neutrophils, macrophages, and other immune cells, may be mediated by cigarette smoking.[39,40] Another study suggested altered leukocyte oxidative metabolism in cigarette smokers,[41] implying a more available activation of inflammatory pathways in lung parenchyma in the setting of another offending agent. Increased reactive oxygen species and associated oxidative cell injury have also been established in cigarette smokers.[42–44] A human study showed that altered neutrophil washout in lung microvasculature and associated lung injury were increased in active cigarette smokers.[39] Furthermore, an in vitro human cell study demonstrated an impaired lung repair mechanism in cigarette smokers resulting from inhibition of fibroblast chemotaxis and proliferation.[45] Collectively, these data from preclinical studies support the hypothesis that a history of cigarette smoking in pancreatic cancer patients who receive gemcitabine-based treatment may increase the risk of GRP via multiple mechanisms. Multiple epidemiologic studies have investigated the prevalence of smoking in pancreatic cancer patients. A pooled analysis of epidemiologic studies reported an approximately 61% rate of cigarette smoking in a pancreatic cancer

population.[46] An earlier prospective study also reported cigarette smoking in approximately 65% of pancreatic cancer patients.[47] Whether the difference in rate of smoking that we observed (75% vs. 61% in these other studies) denotes an increased risk of GRP related to cigarette smoking warrants further prospective studies.

The evidence from the current state of the science strongly suggests that alcohol misuse is also associated with an increased risk of acute lung injury.[48,49] In a recent human study, depleted epithelial lining glutathione concentration, which is one of the characteristic findings of acute respiratory distress syndrome, has been demonstrated in patients with chronic alcohol abuse compared to nonalcoholic controls.[50] In an animal study, it has been demonstrated that surfactant phospholipid secretion is impaired in rats that ingested ethanol.[51] In another animal study, an impaired alveolar epithelial barrier in rats exposed to ethanol was due to altered glutathione function.[52] Collectively, these data support the hypothesis that a history of alcohol consumption is potentially relevant to the development of GRP. Specifically, we observed a history of significant alcohol use in 6 (21%) of our patients who had GRP.

To our knowledge, our review here is the largest report of GRP patients in pancreas adenocarcinoma in the literature. Weaknesses of our study include the retrospective nature of the review, associated unknown confounding factors, and an inability to rule out the potential contributing impact of other antineoplastic agents on GRP in patients who received combination treatment, particularly in an emerging era of gemcitabine and nab-paclitaxel therapy.

On the basis of our data, we recommend a high level of clinical alertness for the diagnosis of GRP, and we recommend early pulmonary consultation for pancreatic cancer patients who develop respiratory symptoms during gemcitabine-based treatment, in particular in patients with a history a cigarette smoking and alcohol consumption—factors that may increase the risk of GRP. We do not recommend routine follow-up lung imaging such as chest CT or chest radiograph in patients who receive gemcitabine to assess this toxicity, given its relatively low incidence, apart from imaging performed for routine disease response assessment. However, respiratory symptoms such as dyspnea and cough after gemcitabine treatment should alert clinicians to evaluate patients for possible GRP via an imaging modality, preferably high-resolution chest CT. In addition, unexplained ground-glass findings identified on routine response assessment imaging should lead to the consideration of a diagnosis of GRP. Our data also indicate that patients with advanced disease are at higher risk for GRP, and clinicians should have a high level of alertness in this patient population. Arguably, patients with any history of idiopathic lung disease or interstitial process should be excluded from gemcitabine-based therapy.

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Clinical Practice Points

- GRP is a potentially life-threatening complication of gemcitabine treatment in pancreatic cancer patients. Although the incidence of GRP is relatively low (< 1.1%), it is associated with significant morbidity and mortality.
- The predisposing factors of GRP have not fully elucidated. We identified potential risk factors for GRP in pancreatic cancer patients, including a history of cigarette smoking, alcohol use, and underlying lung disease.
- In addition to background medical and social history, advanced cancer appears to be associated with an increased risk of GRP.
- We recommend high-level clinical alertness and awareness of the risk of developing GRP in patients with respiratory symptoms such as dyspnea and cough who are receiving gemcitabine-based treatment.
- Early pulmonary consultation and cessation of gemcitabine are warranted if sufficient clinical suspicion arises.

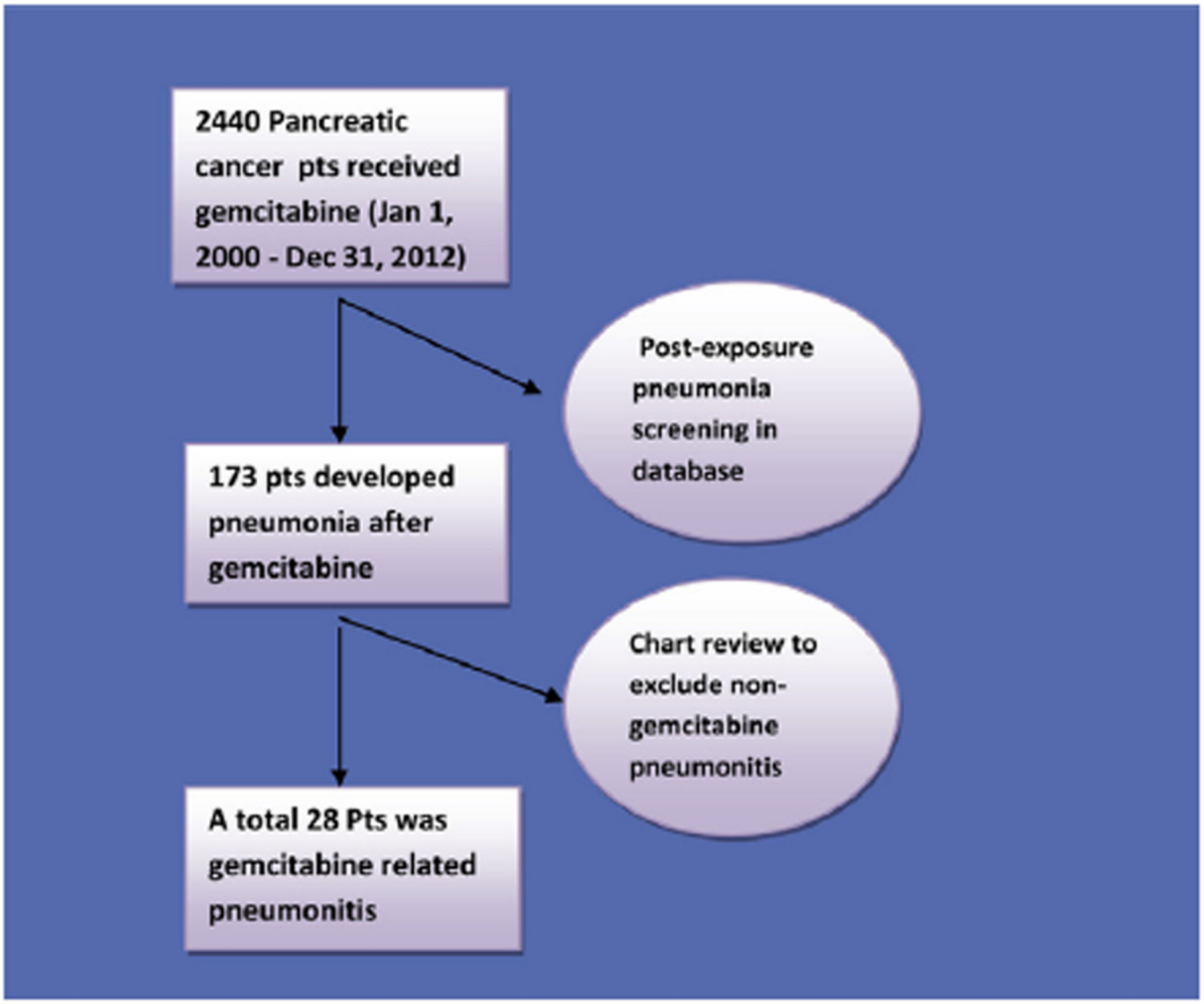

Figure 1.
Patient Disposition

Table 1

Clinical and Demographic Characteristics for Patients With Gemcitabine-Related Pneumonitis

Characteristic	n (%)
Age	
<50 years	3 (10)
50–70 years	12 (42)
>70 years	13 (46)
Race	
White	27 (96)
Other	1 (4)
Gender	
Female	15 (54)
Male	13 (46)
BMI	
Normal	8 (29)
Overweight	15 (54)
Obese	5 (18)
History of Lung Disease	
COPD	4 (14)
ILD	2 (7)
Asthma	0
Disease Status	
Metastatic	20 (71)
Locally Advanced	6 (21)
Adjuvant	2 (7)
Treatment	
Single-agent gemcitabine	18 (64)
Combination therapy	10 (36)
Pneumonitis Grade	
2	7 (25)
3	18 (64)
4	3 (11)
Cigarette Smoking	
Nonsmoker	7 (25)
Active smoker	1 (4)
Former smoker	20 (71)
Alcohol History	
None	11 (39)
Occasional	11 (39)
Regular or heavy	6 (21)

Abbreviations: BMI = body mass index; COPD = chronic obstructive pulmonary disease; ILD = interstitial lung disease.

Table 2

Patient Characteristics

Patient No.	Gender	Age (Years)	BMI (kg/m^2)	Smoker	Alcohol	Prior Lung Disease	Disease Stage	Therapy	Grade of Event	Outcome
1	F	79	19.0	Former	Occasional	–	IV	GC	2	OP/recovery
2	F	73	22.9	Never	Occasional	–	IV	GC	3	IP/recovery
3	F	74	203	Former	Never	–	IV	Gem-E	3	IP/recovery
4	F	51	26.1	Never	Occasional	–	IV	Gem-Ox	4	IP/recovery
5	M	55	33.2	Former	Occasional	–	IV	Gem-Ox	3	IP/recovery
6	M	80	31.5	Former	Never	COPD	IV	GC	3	IP/recovery
7	F	46	21.3	Former	Never	–	IV	GC	2	OP/recovery
8	M	51	29.4	Former	Occasional	–	IV	GC	3	IP/recovery
9	F	80	20.2	Former	Occasional	ILD	IV	GC	3	IP/recovery
10	F	74	23.8	Former	Regular or heavy	COPD	IV	GC	3	IP/recovery
11	M	58	26.5	Former	Regular or heavy	–	IV	GC	2	OP/recovery
12	M	75	26.7	Former	Occasional	–	IV	Gem-E	3	IP/recovery
13	M	41	29.6	Never	Regular or heavy	–	IV	GC	3	IP/recovery
14	F	48	29.8	Former	Occasional	–	IV	Gem-E	3	IP/recovery
15	M	65	27.5	Former	Regular or heavy	–	IV	GC	4	IP/recovery
16	F	70	21.2	Former	Occasional	–	IV	GC	2	OP/recovery
17	F	59	23.1	Former	Never	–	IV	GC	2	OP/recovery
18	F	61	26.9	Former	Never	–	IV	GC	3	IP/recovery
19	M	74	28.5	Former	Never	COPD	IV	GC	3	IP/recovery
20	M	50	29.6	Active	Never	–	IV	GC	3	IP/recovery
21	F	78	28.7	Second hand	Occasional	ILD	III	Gem-Cap	3	IP/recovery
22	M	74	26.9	Former	Never	–	III	Gem-Cap	2	OP/recovery
23	M	74	25.3	Never	Regular or heavy	–	III	Gem	3	IP/recovery
24	F	68	44.5	Never	Never	–	III	GC	2	OP/recovery
25	M	73	26.7	Former	Regular or heavy	COPD	III	Gem-Cap	3	IP/recovery
26	M	60	32.9	Former	Never	COPD	III	GC	4	IP/recovery

Clin Colorectal Cancer. Author manuscript; available in PMC 2016 August 11.

Patient No.	Gender	Age (Years)	BMI (kg/m^2)	Smoker	Alcohol	Prior Lung Disease	Disease Stage	Therapy	Grade of Event	Outcome
27	F	88	25.5	Never	Never	–	IIA	GC	3	IP/recovery
28	F	56	47.4	Former	Occasional	–	IIB	GC	3	IP/recovery

Abbreviations: Cap = capecitabine; COPD = chronic obstructive pulmonary disease; E = erlotinib; GC = gemcitabine; Gem = gemcitabine; ILD = interstitial lung disease; IP = inpatient; OP = outpatient; Ox = oxaliplatin.

Clin Colorectal Cancer. Author manuscript; available in PMC 2016 August 11.

Table 3

Drug Exposure

Patient No.	Total No. of Gemcitabine Doses	Total Cumulative Dose of Gemcitabine (g)	Name of Other Agents (If Applicable)
1	4	4.400	
2	21	33.660	
3	11	16.500	Erlotinib
4	29	52.400	Oxaliplatin
5	1	2.120	Oxaliplatin
6	29	41.900	
7	45	42.700	
8	7	13.600	
9	3	3.900	
10	9	11.700	
11	2	3.900	
12	30	56.100	Erlotinib
13	17	27.500	
14	20	36.400	Erlotinib
15	3	5.700	
16	12	18.500	
17	20	35.000	
18	19	19.400	
19	6	11.800	
20	3	3.800	
21	9	11.700	Capecitabine
22	33	59.400	Capecitabine
23	15	12.500	
24	12	21.900	
25	32	32.800	Capecitabine
26	13	20.500	
27	15	14.300	
28	12	21.200	

Table 4

Literature Pertaining to Gemcitabine-Related Pneumonitis in Pancreatic Cancer

Study	Study Type	No. of Patients	Imaging Findings	No. of Gemcitabine Doses	Treatment	Outcome
Yakabe[33]	Case report	1	Diffuse ground-glass opacities	9	Steroid, neutrophil esterase inhibitor and supportive therapy	Complete recovery
Chi[13]	Case report	1	Diffuse ground-glass opacities	15	Antibiotics and steroid treatment along with supportive therapy	Complete recovery
Shaib[21]	Case report	1	Diffuse ground-glass opacities; cryptogenic organizing pneumonia	2	Antibiotics and steroid treatment along with supportive therapy	Complete recovery
Ishibashi[34]	Case report	1	Diffuse bilateral interstitial infiltrates	6	Steroid treatment along with supportive therapy	Complete recovery
Nomura[35]	Case report	1	Diffuse bilateral interstitial infiltrates	15	Steroid treatment along with supportive therapy	Complete recovery
Hiraya[15]	Case report	1	Diffuse ground-glass opacities	12	Steroid treatment along with supportive therapy	Complete recovery
Tamiya[25]	Cohort series	9	Diffuse ground-glass opacities, thickened septal lines, reticular opacities	Variable	Steroid pulse treatment along with supportive therapy	2 of 9 patients died