Original Study

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

Ibrahim Halil Sahin,[1] Alexander I. Geyer,[2] Daniel W. Kelly,[2] Eileen Mary O'Reilly[2]

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 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.

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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,

[1]Mount Sinai Icahn School of Medicine, St Luke's Roosevelt Hospital Center, New York, NY
[2]Memorial Sloan Kettering Cancer Center, Weill Medical College of Cornell University, New York, NY

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Address for correspondence: Eileen Mary O'Reilly, MD, Department of Medicine, Gastrointestinal Medical Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, Weill Medical College of Cornell University, 300 East 66th Street, Office 1021, New York, NY 10065
Fax: (646) 888-4542; e-mail contact: oreillye@mskcc.org

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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 drug-induced 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,

Figure 1 Patient Disposition