Hosp Pharm 2014;49(9):847–850

www.hospital-pharmacy.com
doi: 10.1310/hpj4909-847

Case Report

Interstitial Pneumonitis from Treatment with Gemcitabine

Brolin B. Poole, PharmD; Leslie A. Hamilton, PharmD, BCPS†; Megan M. Brockman, PharmD, BCPS‡; and Debbie C. Byrd, PharmD, BCPS§*

Abstract

Introduction: The use of gemcitabine may lead to numerous adverse effects ranging from mild to very severe, such as interstitial pneumonitis. The diagnosis of this complication is based on multiple laboratory findings, radiographic evidence, and high clinical suspicion. Presented is a case report of a patient who met these criteria and had onset consistent with drug-induced interstitial pneumonitis.

Case Presentation: A 76-year-old White female was treated with gemcitabine for pancreatic cancer. Two months after the initiation of therapy, she was admitted to the hospital for worsening dyspnea and cough. High clinical suspicion, bilateral interstitial opacities on chest x-ray, worsening pulmonary status, and onset 2 months after initiation of therapy led to the diagnosis of gemcitabine-induced interstitial pneumonitis. Steroid therapy with prednisone was initiated, and the patient's clinical symptoms and radiographic findings improved.

Discussion: Gemcitabine-induced interstitial pneumonitis is well described in the literature. It is a rare but serious complication associated with gemcitabine therapy in which patients present with worsening dyspnea. Most patients only require supportive care and discontinuation of the drug for treatment, but in severe cases supplemental oxygen and steroid therapy must be used before resolution of symptoms. It is important to obtain an accurate medication history to evaluate for other potentially pulmonary toxic medications. Radiographic findings such as bilateral infiltrates should be completely resolved after therapy.

Conclusion: Radiographic findings, clinical symptoms, and clinical suspicion can lead to early recognition of interstitial pneumonitis from gemcitabine. Physician awareness of this adverse effect and early recognition are keys to providing prompt treatment in resolving symptoms and decreasing mortality.

Key Words—gemcitabine, pneumonitis, pulmonary toxicity

Hosp Pharm *2014;49:847–850*

Gemcitabine is an antineoplastic agent used for the treatment of cancers such as non-small-cell lung and pancreatic cancer. Antineoplastic agents are vital to patient outcomes due to the high mortality rate of untreated forms of cancer. Gemcitabine is a pyrimidine antimetabolite that inhibits DNA synthesis thus affecting many organ systems. Common adverse events include myelosuppression, dyspnea, nausea, and vomiting. The severity and duration of dyspnea vary based on individual factors. A severe form of lung toxicity associated with gemcitabine is known as interstitial pneumonitis, which involves acute or chronic interstitial fibrosis of the lung with the tissues becoming stiff and scarred. The fibrosis of the lung interferes with the patient's ability to breathe. The incidence of interstitial

*PGY1 Pharmacy Resident, Department of Pharmacy, University of Tennessee Medical Center, Knoxville, Tennessee; †Assistant Professor, Department of Clinical Pharmacy, University of Tennessee College of Pharmacy, Knoxville, Tennessee; ‡Clinical Pharmacist, Department of Pharmacy, University of Tennessee Medical Center, Knoxville, Tennessee; §Professor and Associate Dean, Department of Clinical Pharmacy, University of Tennessee College of Pharmacy, Knoxville, Tennessee. Corresponding author: Leslie A. Hamilton, PharmD, BCPS, University of Tennessee College of Pharmacy, Knoxville, TN 37920; phone: 865-946-3401; e-mail: lhamilt4@uthsc.edu

pneumonitis from gemcitabine is estimated at 1% to 2% when the drug is used as a single agent in treatment.[1] The incidence may increase when combined with other agents potentially associated with pulmonary toxicity and should be treated early to improve chances of recovery. Underlying pulmonary dysfunction increases the risk of gemcitabine-induced pulmonary toxicity.[2]

The exact mechanism of lung toxicity remains unknown; however, proposed mechanisms have been documented in the literature. One proposed mechanism of toxicity is the release of cytokines in the body, which could result in damage to areas throughout the body. This process could lead to capillary leak syndrome or pulmonary edema.[3]

The diagnosis of interstitial pneumonitis is difficult due to the multiple etiologies of lung dysfunction and should include other likely diagnoses consistent with bilateral interstitial opacities on chest x-ray and worsening respiratory status. Myelosuppression, a common and well-documented adverse event with gemcitabine use, increases the likelihood of acquiring an infection that could decrease lung function.[4]

This article follows a patient who presented with increased cough and dyspnea that progressed to respiratory failure. The patient was diagnosed with interstitial pneumonitis likely secondary to gemcitabine. This case report follows the progression of the illness, the treatment, and her response to treatment.

PATIENT CASE

A 76-year-old White female was sent to the hospital by her primary care physician in February 2012 due to increased cough and shortness of breath. Her medical history was significant for pancreatic cancer, hypertension, atrial fibrillation, anemia, type 2 diabetes mellitus, sleep apnea, gastroesophageal reflux disease, and hypothyroidism. Her surgical history consisted of an appendectomy, cholecystectomy, and a distal pancreatectomy and splenectomy, with excision of her posterior gastric wall 3.5 months prior. She had no history of alcohol abuse, illicit drug use, or smoking. She had no known drug allergies. Her daily medications included lisinopril 20 mg, metformin 1,000 mg, meclizine 75 mg, omeprazole 20 mg, levothyroxine 75 mcg, amiodarone 400 mg, and losartan 50 mg. She also received metoprolol tartrate 25 mg twice daily. Lorazepam 0.5 mg twice daily and prochlorperazine 10 mg every 6 hours were available on an as-needed basis.

She received her first dose of chemotherapy with 1,800 mg of gemcitabine (1,200 mg/m^2) in December 2011 for pancreatic cancer. She was treated once weekly with the dose of 1,800 mg. The patient received 6 doses of gemcitabine prior to admission, having completed her second cycle of therapy (dose once weekly for 3 weeks followed by a 1 week rest).

Upon arrival to the hospital, she had an oxygen saturation of 85% on room air. Her oxygen saturation increased to 89% on 4 L of oxygen. She weighed 127.6 lbs and was 62 in. tall with a body mass index of 29. Her vital signs included blood pressure of 134/63 mm Hg, heart rate of 62 beats per minute, respiration rate of 18 breaths per minute, and temperature of 99°F. Laboratory tests revealed a white blood cell count of 11.2 x10^3/µL (reference range, 4.0-10.0 x 10^3/µL) and a platelet level of 842 x 10^3/µL (150-400 x 10^3/µL). The patient's serum creatinine was 1.07 mg/dL. Radiography of the patient's chest showed bilateral interstitial pulmonary opacities with borderline cardiomegaly.

The patient's initial differential diagnosis included a drug-induced process, possible infection, or pulmonary edema. Diagnosis was believed to be drug-induced interstitial pneumonitis due to gemcitabine and amiodarone, given the radiographical evidence. Both agents were discontinued during evaluation. The patient's treatment course consisted of prednisone 60 mg twice daily on hospital day 6 through hospital day 11. Her lung function improved during the course of therapy until she was able to be taken off oxygen therapy on day 10. Radiography did not show complete resolution but did indicate improvement with the clearance of a significant level of the infiltrates. The patient's blood glucose levels increased while she was on steroid therapy, and she required frequent monitoring and treatment with an insulin sliding scale. She was given a prescription for prednisone 60 mg daily upon discharge and instructed to follow-up with a pulmonologist and her oncologist regarding her pancreatic cancer treatment with gemcitabine because the agent had been discontinued during the visit due to the development of respiratory hypoxia. On a follow-up visit with her physician 1 month after discharge, radiography showed interval improvements in the right pleural effusion. Neither of the presumed offending agents was restarted during the visit; it is unclear whether either agent was restarted in the future.

DISCUSSION

Drug-induced pulmonary toxicity due to cancer treatment with gemcitabine is a well-documented adverse effect. Most adverse events are mild to moderate in severity and require only supportive care.

A MEDLINE search of the literature was performed from 1946 to 2013 to determine the association of gemcitabine and severe pulmonary toxicity requiring hospitalization and treatment with corticosteroids. Search terms were gemcitabine and pneumonitis, gemcitabine and pulmonary toxicity, and adverse effects of gemcitabine. Several reports of gemcitabine-induced pulmonary toxicity were found. One case study revealed interstitial pneumonitis with gemcitabine in combination with cisplatin in which gemcitabine was believed to be the causative agent and required 3 months of steroid therapy.[5] Another case report documented interstitial pneumonitis in a patient who smoked cigarettes when treated solely with gemcitabine. The patient was treated with gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 every 28 days. One week after the second dose, the patient experienced pulmonary complications due to treatment.[6] A case report of a female patient treated for palliation after cancer remission with gemcitabine was diagnosed with interstitial pneumonitis. She received gemcitabine with a dosing regimen of 800 mg/m^2 on days 1, 14, and 28 every 4 weeks for a completion of 1.5 cycles. The patient experienced pulmonary-related complications 8 weeks after the initiation of therapy.[7] Many case reports in the literature show severe pulmonary toxicity in patients receiving combination therapy or treatment for advanced metastatic pancreatic cancer or in patients who had previous lung damage from cigarettes.

The 76-year-old female presenting in our case was admitted shortly after initial therapy with the offending agent, and her lung function rapidly improved once therapy with corticosteroids was initiated. The patient had no known history of pulmonary dysfunction and was on concurrent amiodarone therapy for atrial fibrillation for greater than 5 years when she began chemotherapy. Amiodarone is well documented in the literature to cause pulmonary toxicity including acute respiratory distress syndrome and interstitial pneumonitis. The percentage of patients affected by this adverse event ranges in the literature from 1% to 10%.[8,9] The patient's risk factors for development of pulmonary toxicity from amiodarone included an age greater than 60 years and duration of therapy greater than 6 months.[10] Furthermore, risk of pulmonary toxicity increases at a dose of greater than 400 mg daily; however, it has been documented to occur at lower doses.[11-14] The proposed mechanism of pulmonary toxicity is thought to occur from long-term treatment secondary to accumulation of the drug in the tissues; however, some reports have shown the toxicity occurring at any point during therapy. Although physicians were not able dismiss amiodarone as a potential cause, gemcitabine was ruled as the causative agent by physicians based on the initiation of therapy and onset of symptoms. Previous case reports have shown the onset of symptoms of gemcitabine-induced interstitial pneumonitis to appear within the first few months of therapy. Despite being on amiodarone therapy, the onset of symptoms 2 months after chemotherapy correlated with the onset described in the gemcitabine literature.

Use of the Naranjo adverse drug reaction probability scale in this patient indicated a possible relationship with a score of 4.[15] The patient's improvement from the treatment of corticosteroid therapy increases the likelihood that this was the causative agent. However, neither agent was rechallenged, so ultimate causality was not established.

CONCLUSION

We report a possible case of gemcitabine-induced interstitial pneumonitis. Although there is no specific mechanism identified to cause the damage, proposed mechanisms have been reported. It is unclear why some patients present with severe pulmonary toxicity and others present with a milder form of dyspnea. This patient had no history of underlying lung dysfunction before receiving the drug; however, she was taking amiodarone, which could have exacerbated the effects of gemcitabine. Based on the time period for the initiation of gemcitabine and the long-term use of amiodarone, it was concluded that the offending agent was likely gemcitabine. Increasing awareness of the potential risk of gemcitabine-induced interstitial pneumonitis will better prepare clinicians to recognize and treat this condition early in therapy, which may help prevent associated complications and improve mortality.

REFERENCES

1. Aapro MS, Martin C, Hatty S. Gemcitabine – A safety review. *Anticancer Drugs*. 1998; 9(3):191-201.

2. Umemura S, Yamane H, Suwaki T et al. Interstitial lung disease associated with gemcitabine treatment in patients with non-small-cell lung cancer and pancreatic cancer. *J Cancer Res Clin Oncol*. 2011;137(10):1469-1475.

3. Limper AH. Chemotherapy-induced lung disease. *Clin Chest Med*. 2004;25:53-64.

4. Gupta N, Ahmed I, Steinberg H et al. Gemcitabine-induced pulmonary toxicity: Case report and review of the literature. *Am J Clin Oncol*. 2002;25:96-100.

5. Matsumura E, Ashikari A, Tasaki S. Case of interstitial pneumonia during gemcitabine and cisplatin chemotherapy for locally advanced bladder cancer. *Acta Urologica Japonica*. 2011;57(2):81-85.

6. Shaib W, Lansigan F, Cornfeld D, et al. Gemcitabine-induced pulmonary toxicity during adjuvant therapy in a patient with pancreatic cancer. *J Pancreas*. 2008;9(6):708-714.

7. Ko E, Lee S, Goodman A. Gemcitabine pulmonary toxicity in ovarian cancer. *Oncologist*. 2008;13(7):807-811.

8. Connolly S, Cairns J, Gent M, et al. Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: Meta-analysis of individual data from 6500 patients in randomised trials. Amiodarone Trials Meta-Analysis Investigators. *Lancet*. 1997;350:1417-1424.

9. The CASCADE Investigators. Cardiac arrest in Seattle: Conventional versus amiodarone drug evaluation (the CASCADE study). *Am J Cardiol*. 1991;67:578-558.

10. Ernawati DK, Stafford L, Hughes J. Amiodarone-induced pulmonary toxicity. *Br J Clin Pharmacol*. 2008;66(1):82-87.

11. Wood DL, Osborn MJ, Rooke J, et al. Amiodarone pulmonary toxicity: Report of two cases associated with rapidly progressive fatal adult respiratory distress syndrome after pulmonary angiography. *Mayo Clin Proc*. 1985;60:601-603.

12. Dusman RE, Stanton MS, Miles WM, et al. Clinical features of amiodarone-induced pulmonary toxicity. *Circulation*. 1990;82(1):51-59.

13. Fabiani I, Tacconi D, Grotti S, et al. Amiodarone-induced pulmonary toxicity mimicking acute pulmonary edema. *J Cardiovasc Med (Hagerstown)*. 2011:12(5);361-365.

14. Martin WJ 2nd, Rosenow EC 3rd. Amiodarone pulmonary toxicity. Recognition and pathogenesis (Part I). *Chest*. 1988;93:1067.

15. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981;30:239-245. ■