

LETTER

First Case Report Associating Gemcitabine with Hypersensitivity Reaction in a Patient with Pancreatic Cancer

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Dear Sir:

Gemcitabine (Gemzar®; Eli Lilly and Company, Indianapolis, IN, USA) is a nucleoside analogue indicated as first-line treatment for patients with locally advanced (unresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas [1]. In 1997 Burris *et al.* reported the results of the pivotal phase III study that showed superior clinical benefit response and improved median survival in a randomized comparison with 5-fluoracil (5-FU) and since then is widely accepted as the standard palliative treatment for pancreatic cancer [2]. Recently the Charité Onkologie (CONKO-001) study, a randomized trial of adjuvant chemotherapy in resected pancreatic cancer consisting of gemcitabine versus observation alone showed that gemcitabine significantly delayed the development of recurrent disease [3]. Therefore gemcitabine also promises to become the new standard treatment in the adjuvant setting [3].

Gemcitabine is a well-tolerated cytostatic agent with a mild toxicity profile that allows its combination with other agents [4]. Its toxic effects are myelosuppression, nausea and vomiting, flu-like syndrome, altered liver function tests, proteinuria, hematuria, bronchospasm, somnolence, alopecia, rash, itching, and fever [1, 2, 3, 4]. Cutaneous reactions are well known but are rarely reported [5, 6, 7, 8]. Some case reports refer to gemcitabine-induced erysipeloid rash in areas of previous radiation or lymphangitis, scleroderma-like reactions, linear IgA bullous dermatosis, toxic epidermal necrolysis and Steven-Johnson syndrome [5, 6, 7, 8].

In this report, we present a case of hypersensitivity reaction in a patient with metastatic adenocarcinoma of the pancreas treated with gemcitabine. This is highly important because there are no previous case reports of gemcitabine induced hypersensitivity reaction published in English medical literature and gemcitabine remains considered the most active single agent in the treatment of resected, locally advanced as well as metastatic pancreatic cancer.

The patient is a 56-year-old female with no significant past medical history (allergy to sulfa, causing rash), non smoker, who initially presented to her primary care physician in May of 2008 after experiencing abdominal discomfort associated with laughing. The physical exam was positive for tenderness in the right upper quadrant which prompted a CT scan of the abdomen. The CT revealed a 1.9x3.4x2.2 cm mass within the body of the pancreas with multiple scattered low density lesions within the pancreatic head, uncinate process and pancreatic tail ranging from several millimeters to 1.6 cm. The CT scan also showed marked irregularity and prominence of the omentum compatible with omental caking/seeding and peritoneal metastasis. Pathology review from an ultrasound guided FNA of the omentum showed metastatic adenocarcinoma, favoring pancreatic primary. The patient was staged as T3, N1 M1, and Stage IV. Cytokeratin 7 and cytokeratin 20 markers were positive, whereas estrogen receptor and transcription termination factor, RNA polymerase I (TTF-1) were negative.

The patient began treatment with gemcitabine cycle 1 day 1 at a dose of 1,000 mg/m² weekly (2 weeks on, 1 week off) diluted in 250 mL of normal saline, infused over 30 minutes and the patient was premedicated with dexamethasone 10 mg and ondansetron 8 mg i.v.. Approximately 7 minutes into the infusion of gemcitabine, she experienced throat tightness, sneezing, and developed a hive on her right eyelid (angioedema). She had no shortness of breath, wheezing, nausea, vomiting, abdominal pain, or diarrhea, and no other hives appeared. Her vital signs

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remained stable. The patient was treated with diphenhydramine 25 mg, famotidine 20 mg i.v., hydrocortisone 100 mg i.v. and transferred to the hospital via an ambulance for further observation. During the hospital visit for the next 24 hours, the patient remained asymptomatic. Chemistries, including liver function tests, were within normal limits; LDH was 144 IU/L (reference range: 105-333 IU/L) and albumin was 4.1 g/dL (reference range: 3.5-5.0 g/dL). Complete blood count showed a white count of 6,000 mm⁻³ (reference range: 4.0-10.0 mm⁻³), hemoglobin was 13.0 g/dL (reference range: 12.0-16.0 g/dL), hematocrit 42% (reference range: 37-47%), platelets 251,000 mm⁻³ (reference range: 150,000-350,000 mm⁻³) with a normal differential.

Because of the fact that gemcitabine is the only chemotherapeutic agent approved by FDA for use in advanced pancreatic cancer, we decided to re-challenge the patient with gemcitabine after consenting the patient and administering premedications. The patient returned the following week for the second dose of gemcitabine. She received diphenhydramine 25 mg i.v., famotidine 20 mg i.v. in addition to dexamethasone 10 mg and ondansetron 8 mg i.v.. She only developed few episodes of sneezing without any angioedema, shortness of breath or wheezing. An extra dose of diphenhydramine 25 mg i.v. was given and she received remainder of gemcitabine no further symptoms. She was monitored for approximately 6 hours in the clinic. The patient was instructed to contact emergency (911) if symptoms of hypersensitivity reaction recur at home.

Before challenging her further with gemcitabine, it was decided to premedicate her with *po* diphenhydramine starting a night before and premedicate with i.v. diphenhydramine hydrochloride, famotidine, and dexamethasone 20 mg prior to gemcitabine. She tolerated gemcitabine without further problems. Unfortunately, the patient developed rapid deterioration of her clinical status ad liver failure. She died the following month. No autopsy was performed.

Gemcitabine typically has minimal side effects. When used as a single agent, myelosuppression is the principal dose-limiting toxicity, but less than 1% of patients discontinued therapy for anemia, leukopenia, or thrombocytopenia. Other common side effects are nausea and vomiting (69%), diarrhea (19%), transient elevation of serum transaminases (70%), fever (41%), dyspnea (23%); mild proteinuria (0.5%) and hematuria were seen but were rarely clinically significant.

As per gemcitabine prescription information, bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely as per drug insert [1]. Previous reports have shown that gemcitabine has minor cutaneous reactions but hypersensitivity reaction has not been reported. Severe dyspnea occurred in some patients, with grade 3

toxicity reported in 1.2% and grade 4 in one patient. The dyspnea generally occurred within a few hours of gemcitabine administration and usually lasted for a short time (1-6 hours).

According to the characteristic clinical features, we diagnosed the patient as having an acute hypersensitivity reaction induced by gemcitabine treatment. The lack of previous attack history, the close relationship between administration for chemotherapeutic agents and onset of skin lesions, as well as a no recurrence of them after discontinuation of chemotherapy, all led to the suspicion of a chemotherapy-induced skin reaction.

To our knowledge, this is the first case report associating the nucleoside analogue gemcitabine with hypersensitivity reaction in a patient with pancreatic cancer in the scientific English literature. The potential hypersensitivity reaction of gemcitabine should be borne in mind and considered in further treatment decisions with the increasing use of gemcitabine in different cancer populations. Gemcitabine should not be administered to patients with a known hypersensitivity to this drug.

Conflict of interest The authors declare no conflicts of interest

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