

REPLY

Pulmonary Toxicity Associated with Gemcitabine

Muhammad Wasif Saif

Yale University School of Medicine. New Haven, CT, USA

Gemcitabine (2',2'-difluoro-s'-deoxycytidine; Gemzar[®], Eli Lilly, Indianapolis, IN, USA), a pyrimidine nucleoside analogue similar to cytarabine, inhibits DNA synthesis both by halting DNA replication through the incorporation of its active form into DNA and also by inhibiting ribonucleotide reductase and deoxycytidine monophosphate deaminase [1, 2]. It is administered as a prodrug that becomes phosphorylated by deoxycytidine kinase to the active diphosphate and triphosphate forms [3]. Gemcitabine has been used to treat cancers including non-small cell lung, pancreatic, urothelial, breast, and ovarian cancer [1, 3]. Common side effects include nausea and vomiting, rash, fever, reversible elevation of liver transaminases, flu-like symptoms, and peripheral edema [3, 4]. Myelosuppression is the most common dose-limiting toxicity [3]. Overall, gemcitabine is relatively well tolerated. However, reports describing gemcitabine-induced lung toxicity are increasing [1, 2, 3, 4, 5, 6, 7]. Recently, this toxicity was reported in patient with pancreatic cancer [2, 8, 9]. We reported a 68-year-old man being treated for stage IIa pancreatic cancer after pancreaticoduodenectomy developed hypoxemic respiratory distress after the second dose of gemcitabine 1,000 mg/m² [10]. The radiographic findings on computed tomography scans evolved from ground glass opacities to findings suggestive of cryptogenic organizing pneumonia over the course of two weeks. He was treated with antibiotics, steroids, nebulizers and oxygen. A follow-up computed tomography scan of chest four weeks after presentation showed complete resolution of pneumonitis [10].

In this issue of JOP. J Pancreas (Online), Hiraya *et al.* presents another report of gemcitabine-induced pulmonary toxicity in a patient with pancreatic cancer [11]. Their patient developed pulmonary toxicity after

the 4th cycle and the authors suggest that it may be related cumulative dose. The authors accept that there were no changes in laboratory values with regard to renal and liver function just prior to first cycle and values at cycle number 4. Therefore, no strong relation between cumulative dose of the drug and development of pneumonitis can be claimed at present.

Up to 23% of patients treated with gemcitabine may develop dyspnea; a small fraction of patients may develop severe dyspnea, diffuse alveolar damage, acute respiratory distress syndrome, interstitial pneumonitis, or noncardiogenic pulmonary edema requiring steroid therapy [2, 4, 5, 8, 12]. The incidence of grade 4 lung toxicity, called "Gemzar[®] lung", ranges between 0.06%, as reported by an industry study based on commercial exposure worldwide, and 8%, as reported in several case study reviews. The outcome of Gemzar[®] lung varies from recovery to death [2, 3, 4, 5, 9]. In a review by Barlési *et al.*, the mortality rate was 20% [8].

It is important to remind that gemcitabine-induced lung toxicity is a diagnosis of exclusion. Alternative conditions must be ruled out, including pneumonia, pulmonary embolus, cardiac-related respiratory distress, malignancy, lymphangitic carcinomatosis, and exacerbation of chronic lung conditions. The diagnosis, nevertheless, must be made promptly, or Gemzar[®] lung may be quickly fatal. Clinicians must be cognizant of this condition to prevent further morbidity and mortality in these cancer patients.

Conflict of interest The authors have no potential conflicts of interest

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Correspondence Muhammad Wasif Saif

Yale Cancer Center, Yale University School of Medicine, 333 Cedar Street, FMP 116, New Haven, CT, USA
Phone: +1-203.737.1569; Fax: +1-203.785.3788
E-mail: wasif.saif@yale.edu

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