JOP. J Pancreas (Online) 2009 Sep 4; 10(5):573-575.

LETTER

Gemcitabine-Induced Hepatitis in a Pancreatic Cancer Patient Receiving Adjuvant Therapy following Metastasectomy

Hamid Saadati, Jennifer Peccerillo, Kristin Kaley, Michael L Schilsky, Muhammad Wasif Saif

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

Dear Sir:

Gemcitabine is the only FDA-approved cytotoxic agent for the treatment of pancreatic cancer. Although a relatively safe drug, the major side effects of gemcitabine include bone marrow suppression and flu-like symptoms. Transient abnormalities of liver transaminase enzymes are seen in two-third of patients; elevations of alkaline phosphatase and bilirubin are less common, but severe hepatic toxicity is uncommon. We describe a case of patient with metastatic pancreatic cancer who developed severe gemcitabine-induced hepatitis.

Our patient is a 68-year-old Caucasian male who was initially diagnosed with pancreatic cancer. A CT scan of the chest and abdomen revealed no evidence of metastatic disease. He underwent a Whipple procedure on December 5, 2003. Findings included a moderately differentiated adenocarcinoma measuring 3.7 cm and invading into the pancreatic parenchyma (where there was evidence of chronic pancreatitis) and into the duodenal wall. There was evidence of lymphovascular invasion and extensive perineural invasion with 5 of 19 lymph nodes involved. The gallbladder and all margins were negative. The patient had an uncomplicated postoperative course. At that time he was staged as IIB. He was treated with adjuvant chemotherapy with gemcitabine for 3 cycles in January 2004. He shortly after was found to have liver metastasis after a CT scan was performed for restaging and he was started on gemcitabine in combination with oxaliplatin (GemOx) in February 2004. His last CT of the abdomen and pelvis performed on May 25th, 2004 showed that the liver lesions had regressed. He continued GemOx until January 2005 and staging imaging confirmed no evidence of cancer. The patient remained in remission through November 2008 with serial CA 19-9, and CT scan performed at intervals per National Comprehensive Cancer Network (NCCN) guidelines (http://www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf).

Subsequent CT scan made in November 2008 revealed an enlarging right upper lobe nodule in the lung for which he underwent a right upper lobe lobectomy. The pathology of the nodule revealed well-differentiated mucinous pancreatic adenocarcinoma consistent with his primary tumor. Due to an excellent disease free interval following gemcitabine, he was offered re-treatment with this agent. The patient began adjuvant therapy with gemcitabine, tolerating the first five cycles very well with only grade 1 nausea and grade 1 fatigue. On day 1 of cycle 6, he presented to the clinic with elevated liver functions tests. Before this presentation, his liver functions tests were normal (Figure 1). He reported having no symptoms other than dark urine and denied any change in sensorium, jaundice, abdominal pain, fever or chills, or vomiting. He denied the recent use of any other medications, recent travel or unsafe sexual behaviors. He denied using any herbal products or supplements, acetaminophen, and admitted to only rare minimal alcohol use, the last over two weeks prior to his admission.

Due to severe worsening liver tests, he was admitted to the hospital with the concern that his acute liver injury would become liver failure. At the time of admission to the hospital, his tests were as follows: AST 1,730 U/L (reference range: 0-35 U/L); ALT 1,660 U/L (reference range: 0-25 U/L); total bilirubin 3.69 mg/dL (reference range: 0-1.20 mg/dL); direct bilirubin 2.51 mg/dL (reference range: 0-0.20 U/L); and alkaline phosphatase 226 U/L (reference range: 30-130 U/L). His coagulation studies and albumin were normal. His INR was followed serially over time along with his liver tests. His hepatitis panel and HIV antibody were

Received July 3rd, 2009 - Accepted July 5th, 2009

Key words gemcitabine; Hepatitis; Neoplasm Metastasis; Pancreatic Neoplasms

Abbreviations GemOx: gemcitabine in combination with oxaliplatin

Correspondence Muhammad Wasif Saif
Yale University School of Medicine, Section of Medical Oncology
333 Cedar Street; FMP 116, New Haven, CT 06520, USA
Phone: +1-203.737.1569; Fax: +1-203.785.3788
E-mail: wasif.saif@yale.edu

Document URL http://www.joplink.net/prev/200909/07.html

negative. The rest of his infectious work-up showed no evidence for acute infection or viral exposure. An MRI of abdomen showed mild fatty liver infiltration and no pancreatic disease recurrence. Following admission his liver tests trended towards improvement and his INR remained stable (Figure 1). His AST went down to 1,580 U/L, ALT to 1,580 U/L, alkaline phosphatase to 210 U/L, total bilirubin to 3.69 mg/dL and direct bilirubin to 2.31 mg/dL in the setting of intravenous hydration. His INR on admission was normal and his INR on the morning of discharge was minimally changed at 1.24. Patient was hydrated with intravenous fluids. Ultimately, patient's liver enzymes continued to trend towards improvement throughout the course of hospitalization (Figure 1) and he remained asymptomatic. He was evaluated by the Hepatology Service as well and given the lack of other inciting agents, it was thought that the likely cause of his transaminitis was his treatment with gemcitabine. Therefore, the decision was made to discontinue further therapy with gemcitabine. The patient remained asymptomatic throughout the admission and was discharged home. He was advised to abstain from any alcohol use until he recovered completely and to avoid the use any hepatotoxic drugs, including over the counter acetaminophen until his liver tests improved.

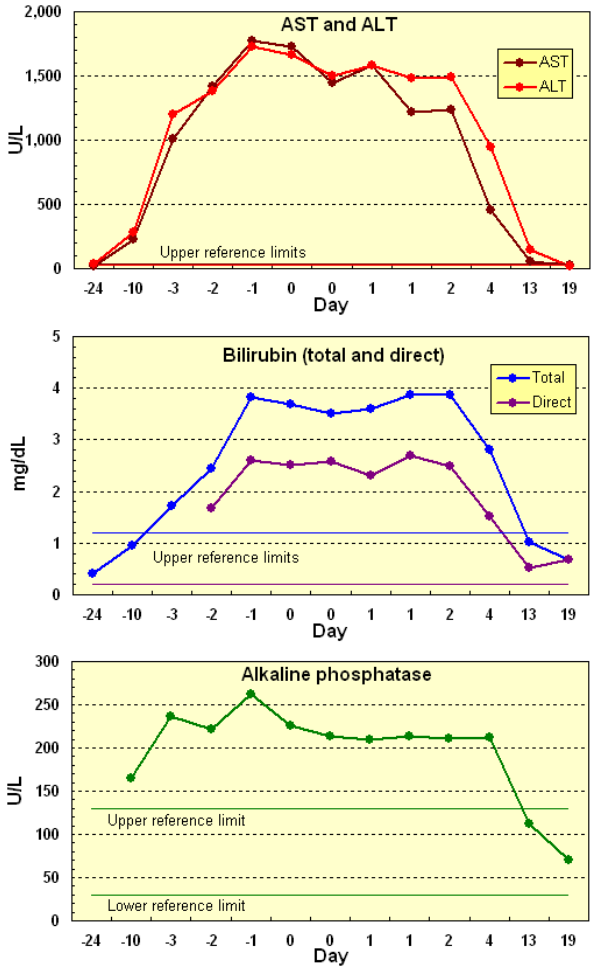

Figure 1. Behavior of liver function tests.

Upon follow-up as an out-patient, his liver tests continued to improve and became normal after seven weeks.

Gemcitabine (difluorodeoxycytidine; dFdC) is the only cytotoxic agent approved by FDA for the treatment of advanced pancreatic carcinoma. It is also useful in non small cell lung carcinoma, breast, urothelial and ovarian cancer [1]. Major toxicities of gemcitabine include marrow suppression, and flu-like symptoms. Less common toxicities include (but not limited to): radiation recall [2], erysipeloid skin toxicity [3], acute myocardial infarction [4], atrial fibrillation [5], interstitial pneumonitis [6], respiratory failure [7], hemolytic uremic syndrome [8], severe neurotoxicity [9], vasculitis [10], and reactivation of hepatitis B [11]. Our patient presented with severe tranaminitis in setting of adjuvant therapy with gemcitabine. Although gemcitabine has a relatively safe profile, case reports have shown that it can cause serious liver damage. By exclusion, gemcitabine is the probable causative agent in this patient, although it can never be completely excluded that a combined effect of gemcitabine together with other medications or factors were responsible. Gemcitabine should be included in the differential diagnosis of transaminitis during chemotherapy with this agent. In particular, clinicians treating cancer patients with preexisting liver conditions or metastases should use caution when using gemcitabine. Careful and close monitoring of liver function tests during therapy is warranted since acute liver injury may portend liver failure if treatment is not discontinued.

This issue is even more important now that the use of gemcitabine is extended both in metastatic as well as adjuvant setting for the treatment of pancreatic cancer.

Conflict of interest The authors have no potential conflicts of interest

References

1. Carmichael J. The role of gemcitabine in the treatment of other tumors. Br J Cancer 1998; 78:21-5.

2. Squire S, Chan M, Feller E, Mega A, Gold R. An unusual case of gemcitabine-induced radiation recall. Am J Clin Oncol 2006; 29:636.

3. Zustovich F, Pavei P, Cartei G. Erysipeloid skin toxicity induced by gemcitabine. J Eur Acad Dermatol Venereol 2006; 20:757-8.

4. Bdair FM, Graham SP, Smith PF, Javle MM. Gemcitabine and acute myocardial infarction. Angiology 2006; 57:367-71.

5. Ferrari D, Carbone C, Codeca C, Fumagalli L, Gilardi L, Marussi D, et al. Gemcitabine and atrial fibrillation: a rare manifestation of chemotherapy toxicity. Anticancer Drugs 2006; 17:359-61.

6. Nomura M, Inoue Y, Fujita S, Sakao J, Hirota M, Souda S. A case of drug-induced interstitial pneumonitis after gemcitabine treatment for advanced pancreatic cancer. Gan To Kagaku Ryoho 2006; 33:123-7.

7. Davidoff S, Shah RD, Arunabh T. Gemcitabine-induced respiratory failure associated with elevated erythrocyte sedimentation rate (ESR). Respir Med 2006; 100:760-3.

8. Saif MW, McGee PJ. Hemolytic-uremic syndrome associated with gemcitabine: a case report and review of literature. JOP. J Pancreas (Online) 2005; 6:369-74.

9. Larsen FO, Hansen SW. Severe neurotoxicity caused by gemcitabine treatment. Acta Oncol 2004; 43:590-1.

10. Geisler JP, Schraith DF, Manahan KJ, Sorosky JI. Gemcitabine associated vasculitis leading to necrotizing enterocolitis and death in women undergoing primary treatment for epithelial ovarian/peritoneal cancer. Gynecol Oncol 2004; 92:705-7.

11. Cheong K, Li J, Karapetis CS. Gemcitabine and reactivation of hepatitis B. Med Oncol 2003; 20:385-8.