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Duodenal perforation in a patient with non-small cell lung cancer receiving Pemetrexed-Cisplatin combination

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ABSTACT

Pemetrexed is increasingly used in combination with platinum antineoplastic agents for the treatment of certain lung malignancies. Its use was associated with favorable hematological adverse reaction compared to standard regimens. Non-hematological life-threatening complications such as gastrointestinal perforations are extremely rare with pemetrexed use and tend to develop in the distal bowel in patients at risk. We report the case of a 56-years old Arab male, heavy smoker newly diagnosed with Stage IV non-small cell lung cancer with no comorbidities, treated with pemetrexed-cisplatin combination. Four days after the first cycle of chemotherapy, the patient developed a small duodenal perforation that required emergency laparoscopy repair. Clinicians should have a high index of suspicion should be taken for alimentary tract perforation in patients presenting with acute abdominal pain during pemetrexed therapy.

INTRODUCTION

Pemetrexed (Alimta® Eli Lilly) is a new antifolate chemotherapeutic (1). It is used either as a monotherapy or in combination with platinum-based chemotherapeutic agents for the management of certain lung malignancies. Compared to cisplatin-gemcitabine, a standard treatment for non-squamous Non-Small Cell Lung Cancer (NSCLC), pemetrexed-cisplatin combination yielded comparable efficacy and significantly lower hematological toxicities and alopecia (2). The non-hematological adverse reactions reported with pemetrexed use in phase III trials were similar to reference regimens used for NSCLC treatment. Among these side effects, the most prevalent GI adverse reactions were nausea, vomiting, and constipation, with no reported cases of life-threatening GI complications (2,3). Here, we report a case of a patient who developed duodenal perforation after receiving the first cycle of pemetrexed-cisplatin combination for the management of metastatic NSCLC.

CASE REPORT

A 56-year old Arab male; who was a heavy smoker was diagnosed on 12 December 2010 with stage IV non-squamous NSCLC of the left lung, with metastasis to the spinal canal and right adrenal gland. He was otherwise in a good state of health at time of diagnosis with no significant medical or surgical history. For cancer pain, the patient received tramadol or acetaminophen with codeine tablets (30/325 mg). He denied using aspirin or non-steroidal

anti-inflammatory medications (NSAIDs). Treatment of the patient's cancer was initiated in January 2011 using radiotherapy. Before commencing chemotherapy, the patient was prescribed oral omeprazole to prevent dyspepsia. Folic acid and a cyanocobolamine were started 5 days prior to chemotherapy. On 10 April 2011, the patient started the first of four 21-day cycle of a combination of pemetrexed 500 mg/m^2 and cisplatin 75 mg mg/m^2. As pre chemotherapy medications, the patient received oral dexamethasone (4mg twice daily for 5 days) to ameliorate cutaneous reactions. On 12 April 2011, the patient presented to the emergency department (ED) complaining of vomiting that was managed with intravenous dexamathasone (10 mg) and ondansetron (8 mg). On 14 April, the patient returned to ED with severe epigastric pain of 24-hours duration described as constant and not exaggerated or relieved by eating or pain medication. The patient denied any vomiting or changes in bowel habits or stool color for the previous 2 days. The patient was afebrile, pulse of 129 beats per minute, blood pressure of 88/54 mmHg and respiratory rate of 22 breaths per min and oxygen saturation of 95%. Laboratory studies revealed normal hemoglobin (Hgb) of 161 mg/L and low white blood cells count 3.9 × 10^9/L, and platelets 152 × 10^9/L. On physical examination, the patient had generalized tenderness with guarding and rigidity. His abdomen was evaluated by computed tomography scan, which revealed multiple intra-abdominal pockets of free air that were attributed to a perforated viscus. The patient was briefly stabilized and then taken to the operating room. Emergency surgery was arranged and laparoscopic repair of a perforated anterior first part of the duodenum was performed by suture plication using an omental patch. The duodenum was found mobile and pliable without evidence of chronic inflammation or ischemia. The perforation was small, measuring to 2-3 mm in diameter. The attending surgical team impression of this perforation was "not typical for peptic ulcer disease (PUD)". The patient had an uneventful recovery and was discharged home on postoperative day 5.

DISCUSSION

Chemotherapy induced GI complications may occur at any stage during cancer treatment. Upper alimentary tract perforations have been also reported in patients receiving antineoplastic agents for the treatment of non-GI malignancies. (4) Pemetrexed is a new chemotherapeutic agent indicated for lung cancer treatment with a favorable hematologic toxicity profile. Serious GI complications with pemetrexed are relatively rare, and tend to develop in patients with underlying GI diseases or receiving concurrent chemotherapeutic agent with high GI toxicity profile. In one phase II study, patients with NSCLC were randomized to two regimens consisted of pemetrexed, carboplatin, and bevacizumab with or without enzastaurin. Both a history of diverticulitis and radiotherapy are risk factors for GI perforations. (5,6) The patient in our case had no history of PUD or other chronic GI disease predisposing him to perforations. His normal Hgb before chemotherapy administration was not consistent with an asymptomatic chronic bleeding ulcer that could precede perforation in patients with PUD. Although our patient had a metastatic disease, it had not extended to his GI tract. Receiving radiotherapy is identified as a risk factor for perforations; however, in our patient, it was not directed to the patient's abdomen. Moreover, the pathology of radiation injuries involves ischemic changes that often appear similar to the alterations observed with arterial thromboembolic event, (7) a pathological picture that was not encountered during the surgical exploration of our patient. In one study that described PUD perforations, the mean size of perforated duodenal ulcers was 9.9 ± 2.1 mm (8), while the duodenal perforation in

our patient was far smaller in size. Also, chronic inflammatory changes, the hallmark of perforated ulcers, were absent making PUD an unlikely etiology of this case. Ulceration induced solely by corticosteroids use continues to be debated, with many studies concluding that corticosteroids impact on gastro-duodenal mucosa develop upon their combination with NSAIDs (9). Systematic chemotherapy induced gastro-duodenal perforations etiology is unknown and could be complex. Both chemotherapy and corticosteroid injury to the GI tract is thought to result from interference of with the normal mechanisms of bowel lining repair by inhibition of reparative inflammatory response, including atrophy of lymphocytes and inhibition of antibodies (10). Chemotherapy also inhibits rapidly dividing tissues such as the GI mucosa, causing epithelial ulceration, which could explain the development of perforation in our patent. Other risk factors for development of perforations such as carcinomatosis and bowel obstruction were absent in our patient. Cigarette smoking could induce GI toxicity via its ulcerogenic effect, however, was not evident in our patient. In addition, omeprazole given to our patient for the prior 3 weeks would help in healing any asymptomatic ulcers even in the presence of adverse prognostic influences such as smoking. The clinical and surgical findings observed in our patient after the first cycle of chemotherapy administration, in the absence of other risk factors for duodenal perforation lead us to conclude that the duodenal perforation in our patient was a consequence of chemotherapy administration. Because the role of pemetrexed in the treatment of malignancy continues to expand, clinicians must be aware of this possible severe GI complication in patient's receiving pemetrexed containing chemotherapy regimen.

REFERENCES

1. Shih C, Chen VJ, Gossett LS, Gates SB, MacKellar WC, Habeck LL, Shackelford KA, Mendelsohn LG, et al. LY231514, a pyrrolopyrimidine-based antifolate that inhibits multiple folate-requiring enzymes. Cancer Res 1997;57: 1116-1123
2. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. Clin Oncol. 2008;26:3543-3551
3. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, Gatzemeier U, Boyer M, Emri S, Manegold C, Niyikiza C, Paoletti P. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 2003;21:2636-2644
4. Liaw CC, Huang JS, Wang HM, Wang CH. Spontaneous gastroduodenal perforation in patients with cancer receiving chemotherapy and steroids. Report of four cases combining 5-fluorouracil infusion and cisplatin with antiemetics dexamethasone. Cancer. 1993;72:1382-5
5. Casey EM, Harb W, Bradford D, Bufill J, Nattam S, Patel J, Fisher W, et al. Randomized, double-blinded, multicenter, phase II study of pemetrexed, carboplatin, and bevacizumab with enzastaurin or placebo in chemonaïve patients with stage IIIB/IV non-small cell lung cancer: Hoosier Oncology Group LUN06-116. J Thorac Oncol. 2010;5:1815-1820
6. Shen X, Denittis A, Werner-Wasik M, Axelrod R, Gilman P, Meyer T, Treat J, Curran WJ, Machtay M. Phase i study of 'dose-dense' pemetrexed plus carboplatin/radiotherapy for locally advanced non-small cell lung carcinoma. Radiat Oncol. 2011;6:17

7. Haboubi NY, Schofield PF, Rowland PL. The light and electron microscopic features of early and late phase radiation-induced proctitis. Am J Gastroenterol. 1988; 83:1140-1144
8. Horowitz J, Kukora JS, Ritchie WP Jr. All perforated ulcers are not alike. Ann Surg. 1989;209:693-696
9. Conn HO, Poynard T. Corticosteroids and peptic ulcer: meta-analysis of adverse events during steroid therapy. J Intern Med. 1994; 236:619-632
10. Warshaw AL, Welch JP, Ottinger LW. Acute perforation of the colon associated with chronic corticosteroid therapy. Am J Surg. 1976;131:442-446