

Oxaliplatin-induced Pancreatitis: A Case Series

WASEEM BUTT¹, HAMID SAADATI² and MUHAMMAD WASIF SAIF^{3,4}

¹Wright State University, Department of Medicine, Dayton, OH, U.S.A.;

²Medical Oncology, Yale University, New Haven, CT, U.S.A.;

³Hematology/Oncology and Pancreas Center,

Columbia University College of Physicians and Surgeons, NY, U.S.A.;

⁴New York-Presbyterian Hospital, New York, NY, U.S.A.

Abstract. *Background:* Drug-induced pancreatitis is less common compared to other causes of acute pancreatitis; the incidence ranges from between 0.1% to 2% of acute pancreatitis cases. Among alkylating agents, oxaliplatin has not been reported to be associated with acute pancreatitis. *Patients and Methods:* This case study presents a series of six cases of acute pancreatitis presumably related to exposure to oxaliplatin which had different gastrointestinal malignancies and were being treated with oxaliplatin in combination with other chemotherapeutic drugs. All other related causes of acute pancreatitis were excluded before implicating oxaliplatin as a possible cause. *Results:* In all cases, oxaliplatin was stopped and patients had resolution of their signs and symptoms, along with a decrease in serum amylase and lipase levels. *Conclusion:* Knowledge regarding acute pancreatitis related to oxaliplatin is of paramount importance in order to diagnose cases early and institute effective treatment in patients who are undergoing chemotherapy with this drug.

Oxaliplatin is a third-generation platinum-based alkylating agent. Cisplatin and carboplatin are other platinum-based alkylating agents. The chemical structure of oxaliplatin consists of a square planar platinum center. In comparison to cisplatin and carboplatin, it contains a bidentate ligand 1,2-diaminocyclohexane in place of the two monodentate ammine ligands. It also has a bidentate oxalate group.

The cytotoxicity of oxaliplatin is thought to result from the formation of DNA adducts and inhibition of DNA synthesis in cancer cells. It is used in combination with 5-fluorouracil (5-FU) and leucovorin (LV) as FOLFOX

chemotherapy, primarily for adjuvant chemotherapeutic treatment of stage III, Dukes' C colorectal cancer. Oxaliplatin received approval from the U.S. Food and Drug Administration for the treatment of stage III advanced colorectal cancer in 2002 (1). It has also shown promising results in other gastrointestinal malignancies, namely, esophagogastric, gall bladder and pancreatic cancer (2-5).

The reported side-effects of oxaliplatin include peripheral neuropathy (both acute, reversible and chronic, irreversible), fatigue, stomatitis, nausea, vomiting, diarrhea, neutropenia, thrombocytopenia, increase in transaminases and alkaline phosphatase, ototoxicity, nephrotoxicity, allergic (hypersensitivity) reaction and local damage to connective tissue if the infusion leaks through the vein. Pancreatitis associated with platinum-alkylating agents is rare; however, there are a few published case reports of cisplatin-induced pancreatitis (6, 7). To date, there has not been any reported case of oxaliplatin causing acute pancreatitis. This study reports a series of six cases of acute pancreatitis presumably caused by oxaliplatin.

Patients and Methods

Subjects. All patients were affected with various gastrointestinal malignancies and were receiving chemotherapeutic treatment at the Yale Cancer Center from July 2008 to July 2010.

Pancreatitis diagnosis. Acute pancreatitis was diagnosed as having any two of the following three features: (i) abdominal pain characteristic of acute pancreatitis, (ii) serum amylase and/or lipase ≥ 3 times the upper limit of normal and (iii) characteristic findings of acute pancreatitis on a computerized tomography (CT) scan of the abdomen.

Laboratory measurements. Normal levels of serum amylase at the Yale Cancer Center was 28-100 U/l, and for serum lipase they were <60 U/l.

All other causes of acute pancreatitis, including alcohol, gallstones and other drugs were excluded before patients were suspected of having oxaliplatin-induced pancreatitis.

Correspondence to: Professor M. Wasif Saif, MD, MBBS, Milstein Hospital, Division Hematology/Oncology 177 Fort Washington Avenue, Suite 6-435, New York, NY 10032, U.S.A. Tel: +1 2123054954, Fax: +1 2123053035, e-mail: mws2138@columbia.edu

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Table I. Demographic, laboratory/radiological findings and treatment outcomes.

Case no.	Age (years)	Gender	Type of malignancy	Chemotherapy regimen	Clinical presentation	Radiographic findings (abdominal CT)	Amylase; lipase levels (U/l)	Treatment and outcome
1	71	Female	Metastatic gastric cancer	FOLFOX and bevacizumab	Intermittent RUQ and epigastric pain for 6 days	Head of pancreas inflammatory changes consistent with pancreatitis	226; 184	FOLFOX and bevacizumab were stopped. Next day lipase decreased to 95.6 U/l
2	51	Male	Metastatic pancreatic adenocarcinoma	GEMOX	Obstructive Jaundice and epigastric pain	Mass head of pancreas and duodenal hematoma	327; 708	Oxaliplatin discontinued, gemcitabine dose reduced
3	51	Male	Metastatic gall bladder adenocarcinoma	GEMOX	One week history of sharp abdominal pain radiating to back	Peripancreatic fluid and inflammatory changes consistent with pancreatitis	55; 1800	Oxaliplatin and gemcitabine stopped, lipase decreased to 647 U/l
4	67	Male	Metastatic colon cancer	FOLFOX and bevacizumab	Intractable epigastric pain	6-mm cystic mass in the head of pancreas, pathology negative for malignancy	Lipase: 139	Oxaliplatin discontinued, lipase decreased to 58.6 U/l three days later. Lipase normal one month later
5	67	Female	Adenocarcinoma of the head of pancreas	GEMOX	Two day history of periumbilical and LLQ abdominal pain	Changes of acute pancreatitis with involvement of celiac plexus	Lipase: 96	Oxaliplatin held, gemcitabine discontinued, two days later lipase: 128 U/l, nine days later: 64.3 U/l
6	68	Female	Adenocarcinoma of the pancreatic neck	GEMOX	Abdominal pain	No change in pancreatic mass	188; 289	Oxaliplatin stopped, patient continued only on gemcitabine. Lipase decreased to 87.7 U/l

FOLFOX: LV, 5-FU, oxaliplatin; GEMOX: gemcitabine, oxaliplatin

Results

Patient characteristics, laboratory/radiological findings and treatment outcomes are described in Table I.

Discussion

Oxaliplatin was approved by the FDA to be used in combination with other chemotherapeutic drugs as adjuvant treatment in patients with stage III colon cancer who have had surgery for cancer removal. It was also approved to treat advanced (stage IV) colorectal cancer and in patients whose cancer has recurred after earlier chemotherapy. Oxaliplatin is also commonly used in combination with gemcitabine or 5-FU in pancreatic cancer.

Earlier clinical trials for advanced colorectal cancer by de Gramont *et al.* showed that adding oxaliplatin to the combination of 5-FU and LV led to significant improvement

in disease-free survival than the traditional 5-FU/LV regimens (8). This was subsequently supported by Kuebler *et al.* (9). Moreover, the MOSAIC trial by Andre *et al.* showed that the combination oxaliplatin/5-FU/LV (FOLFOX) improved not only disease-free survival but also overall survival in stage II or III colorectal cancer (10). Recent meta-analysis of six randomized controlled trials performed by Cao *et al.* showed that there is no statistically significant difference in overall survival, progression-free survival and overall response rate between capecitabine plus oxaliplatin vs. 5-FU plus oxaliplatin regimen as first-line treatment for advanced colorectal cancer (11).

The combination of 5-FU and cisplatin used to be the standard adjuvant chemotherapy for previously untreated advanced esophagogastric cancer. However, recently Cunningham *et al.* showed that the combination of oxaliplatin and capecitabine is as effective (2). Recently, Zhao *et al.* also showed that a modified FOLFOX regimen

is active and well-tolerated as first-line chemotherapeutic treatment in advanced gastric cancer for patients over the age of 65 years (3).

With regards to gallbladder and biliary tract cancer, one study showed that gemcitabine and oxaliplatin have good activity in non-gall bladder cancer but poor activity in gallbladder cancer (12), whereas triple therapy as GEMFOX (gemcitabine, oxaliplatin and 5-FU) showed comparable results for response and survival for both advanced bile duct and gall bladder carcinoma but with more toxicity (4).

The management of pancreatic cancer is quite challenging and revolves around gemcitabine as a standard therapy with combinations such as GEMFOX (gemcitabine plus oxaliplatin). This regimen shows some benefit in patients with advanced pancreatic cancer after their disease progressed, following standard gemcitabine treatment (5).

There have been some case reports mentioning cisplatin causing acute pancreatitis (6, 7); however, to date there has been no report of oxaliplatin-induced acute pancreatitis. The reported cases of this study are, therefore, the first ones highlighting the fact that patients undergoing treatment with oxaliplatin need to be warned about the possible side-effect of developing acute pancreatitis. This recognition is of high importance and in such situations oxaliplatin needs to be discontinued in order to avoid the potentially fatal complications of pancreatitis. Further studies are necessary to elucidate whether factors such as certain characteristics of the individuals, the chemical structure of the drug itself or the nature and stage of certain malignancies predispose patients to develop pancreatitis at increased risk.

References

- 1 Ibrahim A, Hirschfeld S, Cohen MH, Griebel DJ, Williams GA and Pazdur R: FDA drug approval summaries: oxaliplatin. *Oncologist* 9: 8-12, 2004.
- 2 Cunningham D, Starling N, Rao S, Cao Y, Liao C, Tan A, Liu L, Mo Z and Gao F: Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 358: 36-46, 2008.
- 3 Zhao JG, Qiu F, Xiong JP, Zhang L, Xiang XJ, Yu F, Yan J, Zhan ZY and Feng M: A phase II study of modified FOLFOX as first-line chemotherapy in elderly patients with advanced gastric cancer. *Anticancer Drugs* 20: 281-286, 2009.
- 4 Wagner AD, Buechner-Stuedel P, Moehler M, Schmalenberg H, Behrens R, Fahlke J, Wein A, Behl S, Kuss O, Kleber G and Fleig WE: Gemcitabine, oxaliplatin and 5-FU in advanced bile duct and gallbladder carcinoma: two parallel, multicentre phase-II trials. *Br J Cancer* 101: 1846-1852, 2009.
- 5 Demols A, Peeters M, Polus M, Marechal R, Gay F, Monsaert E, Hendlitz A and Van Laethem JL: Gemcitabine and oxaliplatin (GEMOX) in gemcitabine refractory advanced pancreatic adenocarcinoma: a phase II study. *Br J Cancer* 94: 481-485, 2006.
- 6 Bunin N, Meyer WH, Christensen M and Pratt CB: Pancreatitis following cisplatin: a case report. *Cancer Treat Rep* 69: 236-237, 1985.
- 7 Tarin F, Camps C, Berrocal A and Vicent JM: Acute pancreatitis caused by cisplatin and vindesine. *Rev Esp Enferm Dig* 85: 224-225, 1994.
- 8 de Gramont A, Figer A, Seymour M, Homerin M, Hmissi A, Cassidy J, Boni C, Cortes-Funes H, Cervantes A, Freyer G, Papamichael D, Le Bail N, Louvet C, Hendler D, de Braud F, Wilson C, Morvan F and Bonetti A: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 18: 2938-2947, 2000.
- 9 Kuebler JP, Wieand HS, O'Connell MJ, Smith RE, Colangelo LH, Yothers G, Petrelli NJ, Findlay MP, Seay TE, Atkins JN, Zapas JL, Goodwin JW, Fehrenbacher L, Ramanathan RK, Conley BA, Flynn PJ, Soori G, Colman LK, Levine EA, Lanier KS and Wolmark N: Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol* 25: 2198-2204, 2007.
- 10 André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F and de Gramont A: Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 27: 3109-3116, 2009.
- 11 Cao Y, Liao C, Tan A, Liu L, Mo Z and Gao F: Capecitabine plus oxaliplatin vs. fluorouracil plus oxaliplatin as first line treatment for metastatic colorectal cancer – meta-analysis of six randomized trials. *Colorectal Dis* 12: 16-23, 2010.
- 12 André T, Reyes-Vidal JM, Fartoux L, Ross P, Leslie M, Rosmorduc O, Clemens MR, Louvet C, Perez N, Mehdud F and Scheithauer W: Gemcitabine and oxaliplatin in advanced biliary tract carcinoma: a phase II study. *Br J Cancer* 99: 862-867, 2008.

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