World Journal of Gastrointestinal Oncology

Online Submissions: http://www.wjgnet.com/1948-5204office
wjgo@wjgnet.com
doi:10.4251/wjgo.v4.i7.181

World J Gastrointest Oncol 2012 July 15; 4(7): 181-183
ISSN 1948-5204 (online)

CASE REPORT

Oxaliplatin induced disseminated intravascular coagulation: A case report and review of literature

Shweta Kurian, Jessica Macintyre, Muzammil Mushtaq, Caio Max Rocha-Lima, Yeon Ahn

Shweta Kurian, Jessica Macintyre, Muzammil Mushtaq, Caio Max Rocha-Lima, Yeon Ahn, Division of Hematology Oncology, Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL 33136, United States
Author contributions: All authors contributed to this case report.
Correspondence to: Shweta Kurian, MD, Division of Hematology Oncology, Sylvester Comprehensive Cancer Center, University of Miami, 1475 NW 12th ave, Suite 3300 (D8-4), Miami, FL 33136, United States. skurian@med.miami.edu
Telephone: +1-305-2431000 Fax: +1-305-2431145
Received: April 26, 2011 Revised: November 1, 2011
Accepted: November 15, 2011
Published online: July 15, 2012

Abstract

Oxaliplatin in combination with a fluoropyrimide is a treatment option for colorectal cancer patients in the adjuvant and metastatic settings. Very few hematological emergencies have been reported associated with Oxaliplatin. These include autoimmune hemolytic anemia, thrombocytopenia and pancytopenia. We present a case report of a patient who developed hematuria and disseminated intravascular coagulation while receiving the second cycle of FOLFOX and bevacizumab for metastatic colon cancer.

Key words: Oxaliplatin; Disseminated intravascular coagulation; Hematological emergencies; Metastatic colon cancer; Platelet count

Peer reviewer: Macaulay Onuigbo, MD, MSc, FWACP, FASN, Department of nephrology, Midelfort clinic, Mayo Health System, Eau Claire, WI 54702, United States

Kurian S, Macintyre J, Mushtaq M, Rocha-Lima CM, Ahn Y. Oxaliplatin induced disseminated intravascular coagulation: A case report and review of literature. *World J Gastrointest Oncol* 2012; 4(7): 181-183 Available from: URL: http://www.wjgnet.com/1948-5204/full/v4/i7/181.htm DOI: http://dx.doi.org/10.4251/wjgo.v4.i7.181

INTRODUCTION

Oxaliplatin in combination with a fluoropyrimide is a treatment option for colorectal cancer patients in the adjuvant and metastatic settings. Very few hematological emergencies have been reported associated with Oxaliplatin. These include autoimmune hemolytic anemia, thrombocytopenia and pancytopenia. We present a case report of a patient who developed hematuria and disseminated intravascular coagulation while receiving the second cycle of FOLFOX 6 (Flurouracil, Leucovorin and Oxaliplatin) and Bevacizumab for metastatic colon cancer.

CASE REPORT

A 66-year Hispanic female was initially diagnosed with colon cancer in 1997. She underwent sigmoid colectomy at that time for a T2 N1 M0 moderately differentiated adenocarcinoma which was then treated with adjuvant chemotherapy with 5-flurouracil (5-FU) and Leucovorin. The patient presented with pulmonary metastasis in 1998 and since then has been on palliative chemotherapy. She started on FOLFOX 6 and Bevacizumab in Feb 2005 and had received about 12 cycles when she developed shortness of breath, chest pain and lower back pain radiating down to both her lower extremities. The chemotherapy was changed to FOLFIRI (Flurouracil, Leucovorin and Irinotecan) plus Avastin as the above symptoms were thought to be a hypersensitivity reaction to oxaliplatin. Upon progression the patient received multiple lines of palliative chemotherapy which included Cetuximab with Irinotecan, Ixabepilone with Sutent, Gemcitabine with ABT-263 and also several compounds in phase I trials.

On July 2010 the patient, due to the lack of other potentially efficacious regimen, was again placed on Modi-

fied FOLFOX 6 (mFOLFOX 6: Oxaliplatin 85 mg/m^2 IV over 2 h, folinic acid 400 mg/m^2 IV over 2 h, 5-FU 400 mg/m^2 bolus IV, 5-FU 2400 mg/m^2 continuous over 46 h, and bevacizumab 5 mg/kg IV over 90 min) after undergoing successful oxaliplatin desensitization. Chemotherapy cycles were to be repeated every 15 d.

Prior to initiation of FOLFOX 6 and Bevacizumab, the patient's white blood cells (WBC) count was 7600/μL, Hemoglobin (Hb) 13.7G/dL and hematocrit (HCT) 40% and she showed normal comprehensive metabolic profile.

She received her first cycle of treatment without any untoward events but following her second cycle she developed gross total hematuria and ecchymosis of the upper extremities a day later. She was hospitalized at another facility and the treating physician noted thrombocytopenia - platelet count reduced to 12 000/μL, anemia and elevated PT/PTT. Following platelet transfusion the patient's platelet count came up to 55 000/μL. She was managed conservatively and discharged a few days later. The patient was hospitalized to receive her third cycle of chemotherapy with mFOLFOX 6 only. No bevacizumab was given. Laboratory work prior to admission for this chemotherapy showed WBC count of 7200/μL, Hb 11.9 G/dL and HCT 37.1%, platelet count of 318 000/μL and normal liver function tests.

While she was receiving the Oxaliplatin the patient developed gross total hematuria, with passage of clots. Oxaliplatin was stopped immediately. Her hemoglobin and hematocrit dropped to 10.5 G/dL and 32.8% respectively, with elevation of bilirubin, mainly the indirect fraction, to 2.9 mg. The WBC count rose acutely at 60 000/μL and PT/PTT were elevated at 18.2 s/25.0 s (ref range PT: 11.4-14 s, PTT 23.8-32.2 s). The international normalized ratio was 1.56, Fibrinogen dropped to 35 mg/dL (ref range: 215-461 mg/dL) and quantitative D dimmer rose to more than 5000 ng/mL (ref range: Below 0.25 ng/mL) on the next day with a lactate dehydrogenase level of 1052 μ/L (ref range: 313-618 μ/L). Additionally, the patient's platelet count dropped to a nadir platelet count of 110 000/μL, 4 d after the Oxaliplatin infusion. The peripheral smear showed red blood cell hypochromasia, anisocytosis and polychromasis with decreased platelets. Urinalysis showed gross hematuria with microscopic observations consistent with 10-25 red blood cells (RBCs) and many RBC casts. A renal ultrasound scan conducted at the same time showed that the right kidney measured 10.7 cm, with normal echogenicity and corticomedullary differentiation and minimal fullness of the pelvis. No renal stone was seen. The left kidney measured 10.8 cm with normal echogenicity and normal corticomedullary differentiation, no hydronephrosis, no focal lesions, no renal stone and an unremarkable bladder. These findings were consistent with disseminated intravascular coagulation (DIC). The patient was managed conservatively with supportive care. Her hematuria resolved without any intervention and she was discharged 4 d later with normalization of her urine analysis and blood work.

DISCUSSION

Oxaliplatin is a third generation platinum-containing anticancer drug with established activity in colorectal cancer, when combined to a fluoropyrimidine, in the adjuvant and metastatic settings[1,2]. It is a water-soluble compound with a diaminocyclohexane platinum carrier ligand. Oxaliplatin induces the formation of platinated DNA adducts and then inhibits DNA synthesis and repair, finally resulting in apoptosis. The diaminocyclohexane platinum carrier ligand has a more effective action on nucleic acid metabolism with less or similar toxicity than the original platinum compound cisplatin[3]. Common adverse effects include nausea, vomiting, diarrhea, myelosuppression (particularly neutropenia and thrombocytopenia), mucositis, and reversible sensory neuropathies with paresthesias and dysesthesias.

Approximately 10%-15% of patients receiving oxaliplatin will develop hypersensitivity reactions, often after multiple cycles of the FOLFOX regimen[4]. Such patients can undergo a desensitization protocol which may be effective, and help the patients to continue to receive the drug[5].

We believe that this is the first reported case of DIC associated with Oxaliplatin infusion. Our patient had an episode of back pain when she first received oxaliplatin in Aug 2005. We do not have documentation of this first event but the back pain may have represented an episode of hematuria. After disease progression despite multiple lines of palliative chemotherapy, rechallenge with Oxaliplatin became the best therapeutic option. The desensitization protocol[5] went well with no untoward reactions to mFOLFOX6 and bevacizumab infusion. However during her second (with bevacizumab) and third (without bevacizumab) cycles of mFOLFOX 6 the patient developed DIC. The postulated mechanism of DIC here is fibrinolysis induced by oxaliplatin.

There are multiple case reports of ITP and Evans syndrome related to Oxaliplatin infusion[6-12]. Very rarely Oxaliplatin has been reported to cause life threatening acute hematological toxicities with decrease of platelet counts[13], in some cases associated with hemolysis and occasionally with neutropenia[12].

The precise immunohematological mechanism causing these cytopenias is not well understood. It is believed that the cytopenias are caused by antibody-drug immune complexes directed against specific receptors located on the RBC or the platelet membranes[9,12,14-16]. Other authors have noticed high levels of cytokines such as interleukin (IL)-6, IL-10 and tumor necrosis factor α, in patients with constitutional-type reactions to oxaliplatin, suggesting that this type of toxicity may be triggered by a massive release of pro-inflammatory cytokines[9,17]. The full development of the toxicity may require the simultaneous activation of both these mechanisms. Thus, the release of cytokines may be responsible for the inflammatory-like systemic symptoms, whilst the immune-mediated mechanism may lead to hemolytic anemia and thrombo-

cytopenia. For these reasons, steroids administered before and after Oxaliplatin infusion may help decrease the risk and the severity of the associated adverse events[18,19].

In conclusion, Oxaliplatin is being used very commonly in colorectal, second-line pancreatic and gastroesophageal cancers. The treating health care providers should be aware of the rare but potentially life threatening adverse events including DIC.

REFERENCES

1 **André T**, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J, Tabah-Fisch I, de Gramont A. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004; **350**: 2343-2351

2 **Goldberg RM**, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, Findlay BP, Pitot HC, Alberts SR. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; **22**: 23-30

3 **Buti S**, Riccò M, Chiesa MD, Copercini B, Tomasello G, Brighenti M, Passalacqua R. Oxaliplatin-induced hemolytic anemia during adjuvant treatment of a patient with colon cancer: a case report. *Anticancer Drugs* 2007; **18**: 297-300

4 **Siu SW**, Chan RT, Au GK. Hypersensitivity reactions to oxaliplatin: experience in a single institute. *Ann Oncol* 2006; **17**: 259-261

5 **Gammon D**, Bhargava P, McCormick MJ. Hypersensitivity reactions to oxaliplatin and the application of a desensitization protocol. *Oncologist* 2004; **9**: 546-549

6 **Beg MS**, Komrokji RS, Ahmed K, Safa MM. Oxaliplatin-induced immune mediated thrombocytopenia. *Cancer Chemother Pharmacol* 2008; **62**: 925-927

7 **Earle CC**, Chen WY, Ryan DP, Mayer RJ. Oxaliplatin-induced Evan's syndrome. *Br J Cancer* 2001; **84**: 441

8 **Sørbye H**, Bruserud Y, Dahl O. Oxaliplatin-induced haematological emergency with an immediate severe thrombocytopenia and haemolysis. *Acta Oncol* 2001; **40**: 882-883

9 **Koutras AK**, Makatsoris T, Paliogianni F, Kopsida G, Onyenadum A, Gogos CA, Mouzaki A, Kalofonos HP. Oxaliplatin-induced acute-onset thrombocytopenia, hemorrhage and hemolysis. *Oncology* 2004; **67**: 179-182

10 **Curtis BR**, Kaliszewski J, Marques MB, Saif MW, Nabelle L, Blank J, McFarland JG, Aster RH. Immune-mediated thrombocytopenia resulting from sensitivity to oxaliplatin. *Am J Hematol* 2006; **81**: 193-198

11 **Pavic M**, Moncharmont P, Sève P, Rigal D, Broussolle C. Oxaliplatin-induced immune thrombocytopenia. *Gastroenterol Clin Biol* 2006; **30**: 797-798

12 **Taleghani BM**, Meyer O, Fontana S, Ahrens N, Novak U, Borner MM, Salama A. Oxaliplatin-induced immune pancytopenia. *Transfusion* 2005; **45**: 704-708

13 **Shao YY**, Hong RL. Fatal thrombocytopenia after oxaliplatin-based chemotherapy. *Anticancer Res* 2008; **28**: 3115-3117

14 **Desrame J**, Broustet H, Darodes de Tailly P, Girard D, Saissy JM. Oxaliplatin-induced haemolytic anaemia. *Lancet* 1999; **354**: 1179-1180

15 **Garufi C**, Vaglio S, Brienza S, Conti L, D'Attino RM, Girelli G, Terzoli E. Immunohemolytic anemia following oxaliplatin administration. *Ann Oncol* 2000; **11**: 497

16 **Chen VM**, Thrift KM, Morel-Kopp MC, Jackson D, Ward CM, Flower RL. An immediate hemolytic reaction induced by repeated administration of oxaliplatin. *Transfusion* 2004; **44**: 838-843

17 **Ulrich-Pur H**, Penz M, Fiebiger WC, Schüll B, Kornek GV, Scheithauer W, Raderer M. Oxaliplatin-induced fever and release of IL-6. *Oncology* 2000; **59**: 187-189

18 **Santodirocco M**, Lombardi V, Fesce C, Palumbo G, Capalbo S, Landriscina M. Life-threatening oxaliplatin-induced acute thrombocytopenia, hemolysis and bleeding: a case report. *Acta Oncol* 2008; **47**: 1602-1604

19 **Benson AB**. Adjuvant chemotherapy of stage III colon cancer. *Semin Oncol* 2005; **32**: S74-S77

S- Editor Wang JL **L- Editor** Hughes D **E- Editor** Zheng XM