Fatal Thrombocytopenia after Oxaliplatin-based Chemotherapy

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Abstract. *Oxaliplatin-related thrombocytopenia is considered rare and mostly self-limited. We present the first reported fatal case due to this complication. A 64-year-old patient with metastatic colon cancer was admitted for his 24th course of chemotherapy with oxaliplatin and 24-hour infusion of fluorouracil and leucovorin. Consciousness changed on the next evening and deteriorated to deep coma within hours. Computed tomography revealed large intracranial hemorrhage with brain herniation. Hemogram showed severe thrombocytopenia, which was considered to be associated with oxaliplatin. The patient died six days later. The incidence of oxaliplatin-related thrombocytopenia may have been underestimated and its severity long neglected. Other hypersensitivity reactions may precede its onset. Early hemogram examination during hypersensitivity reaction to oxaliplatin may provide early diagnosis and the prevention of the possible fatal consequences.*

Oxaliplatin has been extensively applied worldwide for colorectal cancer and other malignancies. Due to its good safety profile, most patients receive therapy in out-patient settings. Common toxicities include peripheral neuropathy, diarrhea and mild myelosuppression. Hypersensitivity reactions to oxaliplatin infusion have been reported, with an occurrence rate of 10-20% (1-3). Most manifestations were mild and self-limited, but severe thrombocytopenia after repeated administrations may develop (4-10). Most reported events were self-limited within days. We here describe a patient with colorectal cancer who developed fatal oxaliplatin-related thrombocytopenia.

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Case Report

A 64-year-old man with metastatic colon cancer had received eight months of chemotherapy with oxaliplatin and 24-hour infusion of fluorouracil and leucovorin. Computed tomography revealed complete response, so chemotherapy was halted. Fifteen months later, liver tumor recurrence with new lung metastases developed. Salvage chemotherapy with the same regimen was resumed. From that time, a total of five episodes of grade 1 to 2 hypersensitivity reaction occurred during infusion. The manifestations included skin rash, tremor and chills. Notably, mild hemoptysis occurred during the 22nd and 23rd infusions. Hemogram was not examined because the symptoms were self-limited.

The patient was admitted for the 24th course. Hemogram on admission revealed normal results (hemoglobin 15 g/dl, platelet 163,000/μl and leukocyte 5,300 /μl). Chemotherapy was administered after adequate premedication, including antihistamines and steroids. One hour after the start of oxaliplatin infusion, the patient complained of acute back soreness without cutaneous symptoms or hemoptysis. The symptoms subsided after prolonging the infusion time. However, hematemesis developed on the next evening. Half an hour later, the patient became lethargic and the pupils were anisocoric. His consciousness soon deteriorated to coma. Emergent head CT revealed a large intracerebral hematoma of the left frontal lobe with mass effect and midline shift. No brain tumors were identified. The patient was intubated and transferred to an intensive care ward. Immediate follow-up hemogram showed a markedly decreased platelet count (4,000/μl), while there was little change in the leukocyte count (3,880/μl). The international normalized ratio was normal, so thrombotic thrombocytopenic purpura or disseminated intravascular coagulation was less likely. A very low haptoglobin level (<18 mg/dl, normal range 30-178 mg/dl) revealed the possibility of concomitant intravascular hemolytic anemia. A direct antiglobulin test result was strongly positive, so an immune-related process was favored. Despite aggressive platelet transfusion, the patient remained in deep coma without brainstem reflexes, and eventually died of multi-organ failure six days after the onset of intracranial hemorrhage.

Table I. *Oxaliplatin-related thrombocytopenia*.

	Hemolysis	Infusion number	Onset (hours)	Preceding symptoms	Treatment	Result
Earle *et al*. (4)	Yes	N.A.	5	Not mentioned	Steroid, transfusion	Recovery
Sørbye *et al*. (5)	Yes	9	1 day	Back pain	Transfusion	Recovery
Dold *et al*. (6)	No	19	4	Skin rash	Transfusion	Recovery
Koutras *et al*. (7)*	Yes	14	1	Fever, chills, nausea, vomiting and back pain	Steroid, transfusion	Recovery
	No	13	1 day	Back pain	No	Recovery
Taleghani *et al*. (8)	Yes	15	4	Not mentioned	Steroid, transfusion	Recovery
Curtis *et al*. (9)	No	17	2 days	Abdominal pain	Transfusion	Recovery
	No	10	24	Not mentioned	Transfusion	Recovery
Pavic *et al*. (10)	No	20	8	Not mentioned	Steroid, transfusion	Recovery

N.A.: Not available. *Steroid was also used as a premedication.

Discussion

We present a case with fatal intracranial hemorrhage due to oxaliplatin-related thrombocytopenia. To our knowledge, this is the first example of a patient to die of this complication. Oxaliplatin is generally used in many malignancies, especially colorectal cancer. Severe oxaliplatin-related thrombocytopenia is rare. In literature, most patients recovered after platelet transfusions or steroid use (Table I). Thrombocytopenia may be associated with hemolytic anemia, but not always (4, 5, 7, 8). All the events recorded developed after repeated infusions; the earliest episode occurred during the ninth infusion (5). The onset is various: it could be as fast as one hour after the start of oxaliplatin (7), but might be delayed to a few days after (5).

Other hypersensitivity reactions frequently preceded manifestations of thrombocytopenia, with back pain most commonly described (5-7, 9). Three out of the nine patients previously reported suffered from acute back pain, an unusual manifestation of oxaliplatin-related hypersensitivity reactions (11). The first discomfort in our patient was also back soreness, which had never happened during the prior infusions. The explanation of this unique association needs more investigation.

Moreover, these preceding symptoms imply that physicians should be cautious with oxaliplatin-related allergic reactions. Although most allergies are self-limited, they may suggest a higher possibility of subsequent severe thrombocytopenia. In one retrospective study, 7.1% of patients with allergic reaction to oxaliplatin developed thrombocytopenia (12). The occurrence rate is probably underestimated because hemograms are not routinely examined during allergic reactions and thrombocytopenia may resolve within days. Our patient deteriorated very fast after hemoptysis. In prevention, hemogram examination during hypersensitivity reactions to oxaliplatin should be considered for those patients with repeated episodes.

The mechanism of oxaliplatin-related thrombocytopenia is considered immune-related. Prior case reports described positive direct antiglobulin test result (4, 5, 7, 8), which was also positive in our patient. Immunoglobulin G antibodies against platelets in the presence of oxaliplatin were indeed identified in four patients (8-10). By monoclonal antibody-specific immunomobilization of platelet antigen assay, GPIIb-IIIa had the only or strongest reaction with the patients' serum compared to the other platelet antigens. However, how oxaliplatin facilitates the reaction between the antibodies and platelets remains unknown. The preference of this immune reaction to GPIIb-IIIa also mandates further exploration.

Due to the considered immune-related nature of oxaliplatin-related thrombocytopenia, steroid was sometimes used as a treatment. Nonetheless, several patients recovered solely by transfusion (Table I). Although used as a premedication, our patient and another described by Koutras *et al*. still developed thrombocytopenia (7). These cases imply steroid had limited effect in preventing allergic events to oxaliplatin.

In summary, we describe a case with oxaliplatin-related thrombocytopenia which resulted in fatal intracranial hemorrhage. Immune-related thrombocytopenia may develop after repeated oxaliplatin exposure. Its onset is frequently preceded by other allergic reactions. Physicians should be cautious when patients have repeated symptoms or signs of allergic reaction to oxaliplatin because severe thrombocytopenia may follow. Early hemogram examination may provide early diagnosis and the prevention of the possible fatal consequences.

References

1 Brandi G, Pantaleo MA, Galli C, Falcone A, Antonuzzo A, Mordenti P, Di Marco MC and Biasco G: Hypersensitivity reactions related to oxaliplatin (OHP). Br J Cancer *89*: 477-481, 2003.

2 Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, Topham C, Zaninelli M, Clingan P, Bridgewater J,

Tabah-Fisch I and de Gramont A: Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med *350*: 2343-2351, 2004.

3 Gowda A, Goel R, Berdzik J, Leichman CG and Javle M: Hypersensitivity reactions to oxaliplatin: incidence and management. Oncology (Williston Park) *18*: 1671-1675, 2004.

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

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

6 Dold FG and Mitchell EP: Sudden-onset thrombocytopenia with oxaliplatin. Ann Intern Med *139*: E156-E157, 2003.

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

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

9 Curtis BR, Kaliszewski J, Marques MB, Saif MW, Nabelle L, Blank J, McFarland JG and Aster RH: Immune-mediated thrombocytopenia resulting from sensitivity to oxaliplatin. Am J Hematol *81*: 199-201, 2006.

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

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

12 Maindrault-Goebel F, Andre T, Tournigand C, Louvet C, Perez-Staub N, Zeghib N and De Gramont A: Allergic-type reactions to oxaliplatin: retrospective analysis of 42 patients. Eur J Cancer *41*: 2262-2267, 2005.

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