Oxaliplatin-induced immune hemolytic anemia: a case report and review of the literature

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We report a 59-year-old woman diagnosed with metastasic colorectal cancer who developed immune hemolytic anemia during FOLFOX chemotherapy (oxaliplatin/leucovorin/5-fluorouracil). Immunohematologic studies demonstrated that immune hemolysis was oxaliplatin-mediated. On the basis of this case and in a review of the literature in which 13 cases of previously reported oxaliplatin-induced immune cytopenia have been identified, we suggest some clinical clues regarding the use of oxaliplatin in cancer patients. *Anti-Cancer Drugs* 18:973–976 © 2007 Lippincott Williams & Wilkins.

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Introduction

Oxaliplatin, a third-generation platinum compound, is one of the most active drugs in colorectal cancer [1]. Its side effects are usually mild, and consist of hypersensitivity reactions, gastrointestinal symptoms, bone marrow toxicity and, characteristically, sensory neuropathy triggered by cold. Although less frequently, oxaliplatin has been also associated with the development of severe immune cytopenias [2–13]. We describe a case of oxaliplatin-induced immune hemolytic anemia, and review the clinical and biological features of previously published cases of such a complication.

Case report

In September 2000, a 59-year-old woman was diagnosed with transverse colon invasive adenocarcinoma and submitted to segmental colectomy. Liver and celiac lymphadenopathy metastases were identified during laparotomy. She received 12 cycles of modified FOLFOX-4 (fluorouracil bolus 400, folinic acid 200, oxaliplatin 85 mg/m^2 in 2 h and fluorouracil 2400 mg/m^2 continuous infusion in 46 h) with this chemotherapy leading to a complete response; owing to the appearance of neurotoxicity, oxaliplatin dose was reduced in the last FOLFOX cycle. In February 2002, she referred intense lumbar pain and a computed tomographic scan showed enlarged retroperitoneal lymph nodes. Nine cycles of irinotecan, fluorouracil and folinic acid were administered, this resulting in a partial response. Low-back pain reappeared in November 2003 and palliative irradiation was given, again with pain relief. In January 2004, the presence of lumbar pain led to the demonstration of extensive retroperitoneal involvement along with multiple liver metastases. The patient was given modified FOLFOX-4, with dexamethasone 20 mg intravenously before chemotherapy administration. The blood analysis performed 48 h before the administration of the third FOLFOX cycle showed the following values: hemoglobin (Hb) 123 g/l, white blood cell (WBC) count 4.9×10^3/μl and platelet count 202×10^3/μl; the serum creatinine was 1.5 mg/dl. During the infusion of oxaliplatin as part of the third FOLFOX cycle, the patient experienced severe low-back pain; because of this treatment was stopped after infusing 40% of the prescribed dose of this drug. During the next 24 h, pain disappeared but the patient developed hypotension, oliguria, hematemesis and darkly colored urine, which corresponded to the presence of hemoglobinuria. Laboratory studies conducted immediately after stopping oxaliplatin infusion demonstrated Hb 130 g/l, WBC count $41{,}6 \times 10^3$/μl with 75% neutrophils, platelet count 108×10^3/μl, serum creatinine level 1.8 mg/dl (normal value: 0.5–0.9) and lactate dehydrogenase 556 IU/l (normal value < 450). At this time the direct antiglobulin test (DAT) was positive for IgG and C3d/C3b (Diamed-ID, ID-card 'Liss/Coombs'), and the indirect antiglobulin test was negative. Normoblasts, teardrop red blood cells (RBCs) and schystocytes were not seen in the peripheral blood smear, and the coagulation tests were within normal values, this arguing against tumoral bone marrow infiltration, microangiopathic hemolytic anemia and disseminated intravascular coagulation. Over the next week (Fig. 1), platelet counts and Hb levels felt to 7000/μl and 84 g/l, respectively, and serum creatinine level rose to 7.5 mg/dl. She was managed with transfusions of platelets, which did not substantially modify the platelet count (Fig. 1), and packed RBC, parental electrolytic fluids, methylprednisolone and forced diuresis with furosemide. The patient was

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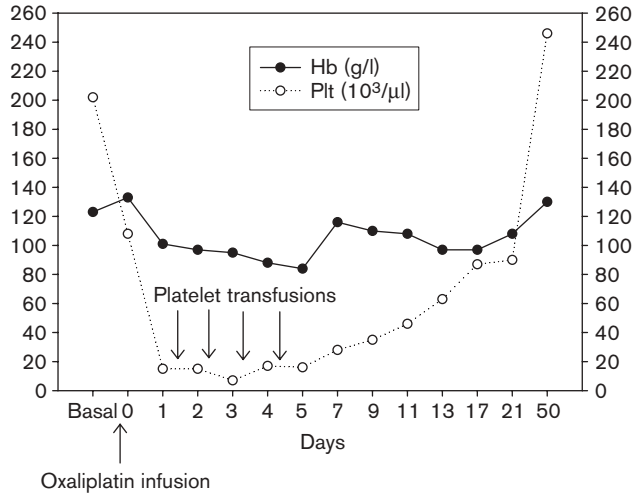
discharged 3 weeks after admission with the following analytical values: serum creatinine level 1.3 mg/dl, platelet count 90×10^3/μl and Hb level 108 g/l. One month later, renal function and blood cell counts were normal (Fig. 1). The patient eventually died in December 2004 owing to tumor progression.

Immunohematologic study

Oxaliplatin-dependent RBC antibodies were investigated in a serum sample taken the day after oxaliplatin infusion. Lyophilized oxaliplatin (Eloxatin; Sanofi-Synthelabo, Notre Dame de Bondeville, France) was diluted to 5 mg/ml with 5% sterile dextrose. From this stock preparation, a working solution at 10 mg/ml was prepared in phosphate-buffered saline (PBS), pH 7.2. Mixtures of patient's serum, oxaliplatin and group 0 RBCs at 3% in PBS were incubated at 37°C for 1 h, visually examined for hemolysis or agglutination after centrifugation, washed three times in 0.9% saline, and submitted to antiglobulin test with either anti-IgG or anti-C3b/C3d (both from Sanquin Pleasmanlaan, Amsterdam, The Netherlands). Controls including serum from healthy group AB donor instead of patient serum and PBS instead of oxaliplatin were run in parallel. As it is shown in Table 1, the antiglobulin test was only positive for IgG in the mixture that contained the patient's serum and oxaliplatin.

Fig. 1



Evolution of hemoglobin (Hb) and platelet count (Plt) after oxaliplatin infusion.

Discussion

In the case herein reported, the abrupt onset of low-back pain during oxaliplatin infusion followed by hemoglobinuria, renal failure and a positive DAT strongly suggested oxaliplatin-related immune-mediated intravascular hemolysis, a diagnosis that was substantiated by the finding of oxaliplatin-dependent RBC antibodies in the patient's serum.

As the first description by Desrame *et al.* [2] in 1999 of a 66-year-old woman suffering from metastatic colorectal adenocarcinoma who developed autoimmune hemolytic anemia during the oxaliplatin infusion of the 41st cycle of FOLFOX, 13 additional cases of oxaliplatin-induced immune cytopenias have been reported [3–12] (Table 2). Most of them correspond to pure autoimmune hemolytic anemia [2,3,7,8,12] and Evan's syndrome [4,5,9], and, more rarely, to immune thrombocytopenia [6,11,13] and immune pancytopenia [10]. The majority of these case reports refer to women with advanced colorectal cancer receiving oxaliplatin-containing regimens. The clinical picture of oxaliplatin-induced cytopenia is characteristically preceded by signs of acute intravascular hemolysis (back pain, hemoglobinuria and renal failure) during drug infusion, followed by the appearance of mucocutaneous bleeding in those cases also showing immune thrombocytopenia (Table 2). The immune reaction triggered by oxaliplatin seems to develop when a relatively high cumulative dose of this agent has been administered. Supportive measures, including corticosteroids and transfusions, may contribute to improve the clinical picture, but the main procedure for abrogating the process is to discontinue the administration of oxaliplatin. It has been suggested that corticosteroids, administered for preventing oxaliplatin-induced vomiting and hypersensitivity, may attenuate the course of oxaliplatin-related immune cytopenias [5,7–9]. In our patient, however, as well as in the case reported by Dold and Mitchell [6], high doses of dexamethasone before oxaliplatin infusion did not prevent the appearance of immune cytopenia.

Table 1 Results of the immunohematologic study

Mixture					Results		
Patient's serum (100 μl)	Healthy AB donor's serum (100 μl)	Oxaliplatin 10 μg/ml (100 μl)	PBS (100 μl)	RBC (40 μl)	Hemolysis	DAT IgG	DAT C3b-C3d
Yes	**No**	**Yes**	**No**	**Yes**	**–**	**–**	**–**
No	Yes	Yes	No	Yes	+	–	–
Yes	No	No	Yes	No	–	–	–

DAT, direct antiglobulin test; RBC, red blood cells; –, negative; +, positive.
The mixture that demonstrates the causative role of oxaliplatin is represented in bold.

Table 2 Characteristics of the patients with oxaliplatin-induced cytopenias

Author (reference)	Gender/age	Type of tumor	Chemotherapy/ cumulative dose of oxaliplatin (g/m^2)	Clinical picture	Thrombopenia/ hemolytic anemia	Renal failure	DAT	Response to treatment[b]
Sanofi [11]	NA	NA	Oxaliplatin/NA	NA	Yes/No	NA	NA	No[c]
Desrame *et al.* [2]	F/66	M colon cancer	FOLFOX/4.1	Back pain/fever/chills/ jaundice/dark urine	No/Yes	Yes	IgG/C3d	No[c]
Garufi *et al.* [3]	F/57	M colon cancer	FOLFOX/1.5	Fever/jaundice/dark urine	No/Yes	No	IgG/C3d	Yes
Earle *et al.* [4]	M/56	M colon cancer	FOLFOX/1.3	Mucous bleeding	Yes/Yes	No	IgG	Yes
Sorbye *et al.* [5]	M/52	M colon cancer	FOLFOX/0.8	Back pain/mucous bleeding	Yes/Yes	No	IgG/C3d	Yes
Sorbye *et al.* [5]	F/40	M colon cancer	FOLFOX/1.1	Back pain	Yes/Yes	No	IgG/C3d	Yes
Dold and Mitchell [6]	F/51	M rectal cancer	Oxaliplatin/1.6	Petechial purpura	Yes/No	No	NA	Yes
Chen *et al.* [7]	F/49	M colon cancer	FOLFOX/1.4	Anemic syndrome/fever/ chills	No/Yes	No	IgG	Yes
Hofheinz *et al.* [8]	M/60	M colon cancer	FOLFOX/1.4	Back pain/jaundice/dark urine	?/Yes	Yes	IgG/C3d	Yes
Koutras *et al.* [9]	F/70	M colon cancer	FOLFOX/?	Back pain/fever/chills/ hematemesis	Yes/Yes	No	IgG/C3d	Yes
Taleghani *et al.* [10]	F/79	Advanced colon cancer	FOLFOX/1.5	Back pain/fever/chills/anemic syndrome/purpura	Yes/Yes[a]	No	IgG/C3d	Yes
Noronha *et al.* [12]	F/59	M colon cancer	FOLFOX/1.6	Back pain/dark urine	Yes/No	No	IgG/C3d	Yes[d]
Curtis *et al.* [13]	F/38	M colon cancer	FOLFOX/NA	Mucocutaneous bleeding	Yes/No	No	NA	Yes
Curtis *et al.* [13]	F/55	M colon cancer	FOLFOX/NA	Mucocutaneous bleeding	Yes/No	No	NA	Yes
Cobo *et al.*	F/59	M colon cancer	FOLFOX/1.2	Back pain/dark urine/ hematemesis	Yes/Yes	Yes	IgG/C3d	Yes

DAT, direct antiglobulin test; F, female; M, male; NA, not applicable.
[a]This patient also had immune neutropenia.
[b]Treatment mainly consisted of corticoesteroids, transfusions (red blood cells, platelets, fresh frozen plasma) and, in some cases, dialysis.
[c]These two patients died as a consequence of oxaliplatin-induced immune cytopenia.
[d]Self-limited.

From a clinical point of view, the relationship between oxaliplatin infusion and immune cytopenia is rather clear in most of the reported cases [10]. The ultimate prove of the oxaliplatin causality in RBC lysis is, as in our case, the demonstration of oxaliplatin-dependent RBC antibodies in patient's serum [2,3,7,8,10]. By exposing the oxaliplatin–antibody–RBC complex to mercaptoethanol [3] or by IgG depletion of patient's serum [7], it has been demonstrated that oxaliplatin-dependent RBC agglutination is mediated by an IgG-type antibody. Lack of cross-reactivity with cisplatin – a platinum family drug that, as well as carboplatin, can induce hemolytic anemia [14–17] – indicates a specific oxaliplatin immuno-allergic process [2].

Although the precise immunohematological mechanisms explaining oxaliplatin-mediated RBC lysis are not well understood, our findings as well as those reported by others [2,3,7,8,10], are consistent with the presence of antibody–drug immune complexes. Regarding the mechanism by which immune complexes interact with specific epitopes on RBC membranes, oxaliplatin–antibody complex binds through its Fab region to a 110-kDa RBC membrane protein, which could correspond to the Band 3 anion channel as it has been described in tolmetin-induced intravascular hemolysis [7,18].

Although less studied, oxaliplatin-induced thrombocytopenia and neutropenia seem to follow a similar mechanism to that responsible for RBC lysis. In this regard, it has been reported that patient's serum reacts against platelets and neutrophils only in the presence of oxaliplatin, indicating the presence of oxaliplatin-dependent antibodies against these blood cell types [10]. Interestingly, oxaliplatin-dependent anti-RBC antibodies do not cross-react with platelets, supporting the idea that oxaliplatin can induce the formation of antibodies with different specificities [10]. More recently, the presence of oxaliplatin-dependent antiplatelet antibodies against glycoprotein IIb/IIIa in two patients with metastatic colon cancer who developed severe thrombocytopenia and bleeding diathesis after being treated with FOLFOX has been demonstrated [13]. Unfortunately, studies for drug-dependent platelet antibodies could not be performed in the present case, but the acute development of extreme thrombocytopenia not responding to platelet transfusions immediately after oxaliplatin infusion suggested peripheral platelet destruction rather than bone marrow toxicity.

After the approval of the FOLFOX regimen in the adjuvant treatment of colorectal cancer [19,20], oxaliplatin is now being increasingly employed. This is likely to increase the number of oxaliplatin-induced immune cytopenia cases, which should be promptly identified. In this regard, the inclusion of indirect hemolysis parameters (reticulocyte count, serum lactate dehydrogenase and serum haptoglobin) as well as DAT in routine analysis of oxaliplatin-treated patients showing anemia and/or thrombocytopenia would be useful to distinguish between drug-induced immune cytopenia and bone

marrow toxicity. Moreover, oncologists should also be aware of the possible development of symptoms and signs of intravascular hemolysis during oxaliplatin infusions, especially of the appearance of low-back pain, which can be easily misinterpreted as infiltrating tumoral pain. Finally, the appearance of an oxaliplatin-induced immune cytopenia makes it mandatory to indefinitely avoid this agent in further treatments in order to prevent this rare but potentially life-threatening adverse effect.

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