Oxaliplatin-induced hemolytic anemia during adjuvant treatment of a patient with colon cancer: a case report

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We report the case of a 64-year-old patient who developed autoimmune hemolytic anemia with thrombocytopenia and acute renal failure shortly after the infusion of the 11th cycle of adjuvant chemotherapy with oxaliplatin, folinic acid and 5-fluorouracil (FOLFOX 4), and was successfully treated by means of plasmapheresis, corticosteroids and dialysis. To the best of our knowledge, only seven other cases have been described in the literature, but we believe this serious adverse event induced by oxaliplatin is more frequent than this would suggest. *Anti-Cancer Drugs* 18:297–300 © 2007 Lippincott Williams & Wilkins.

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Introduction

Oxaliplatin (L-OHP) is a third-generation platinum compound that is active against a wide range of tumors, and is currently used in the treatment of various cancers as a single agent or in combination with, for example, 5-fluorouracil (5-FU) and folinic acid [1]. Its well-known adverse effects include nausea, emesis, diarrhea, myelosuppression (particularly neutropenia and thrombocytopenia), mucositis, and reversible sensory neuropathies with paresthesias and dysesthesias. The onset of immunohemolytic anemia following L-OHP administration was reported in a 66-year-old woman by Desrame *et al.* [2] and in a 57-year-old woman by Garufi *et al.* [3]; since then, sporadic reports of other immune-mediated hematological emergencies have appeared [4].

We describe a case of acute hemolytic anemia complicated by acute renal failure after L-OHP infusion.

Case report

This 64-year-old man was diagnosed as having colon cancer in August 2004 (Dukes/Astler-Coller stage C2; tumor, node, metastasis stage III B) and underwent left hemicolectomy in September 2004. Multiple biopsies showed metastases in only one perivisceral lymph node, and the results of liver ultrasonography and a chest radiogarph were negative. In October 2004, he started adjuvant chemotherapy with L-OHP, infusional 5-fluorouracil (5-FU) and leucovorin every 2 weeks, according to the oxaliplatin, folinic acid and 5-FU (FOLFOX 4) schedule [5], and completed 10 of the 12 programmed cycles with only minor side effects (asthenia, mild hypokalemia and grade 1 thrombocytopenia) [6]; laboratory tests showed that his hematological and renal function remained normal (Table 1). During the 11th L-OHP infusion on 12 April 2005, he complained of transient shivering without fever and sudden back pain. During the following hours, he developed scleral jaundice, followed by subscleral hemorrhaging and, at home, noticed darkly colored urine.

Twenty-four hours after the L-OHP administration, laboratory tests showed high levels of alanine aminotransferase, aspartate aminotransferase, total bilirubin, creatinine, lactate dehydrogenase (Table 1), creatine phosphokinase [260 U/l; normal values (n.v.) 0–170 U/l], γ-glutamyl transpeptidase (212 U/l; n.v. 8–61 U/l), C-reactive protein (126 mg/l; n.v.; 0–10 mg/l) and uric acid (11.6 mg/dl; n.v. 3.4–7.0 mg/dl), and therefore the infusion of 5-FU was stopped. Severe hematuria was observed with hemoglobinuria, albuminuria and reduced renal function values, associated with a progressive reduction in 24-h diuresis. A blood test showed a reduced platelet count, associated with a slight decrease in red blood cells and hemoglobin (Table 1); a peripheral blood smear did not show any schistocytes. A physical examination and fecal occult blood test excluded a gastrointestinal hemorrhage. No signs of consumption coagulopathy (normal international normalized ratio, fibrinogen and activated partial thromboplastin time), but a high D-dimer level (72 μg/ml) suggested activated fibrinolysis. Serum haptoglobin was reduced (below 30 mg/dl) and serum electrophoresis showed a polyclonal rise in IgG values (23.9%; n.v. 11.0–21.0%); a direct Coombs' test was positive, as were direct antiglobulin and IgG antibody tests, but the patient was negative for antiplatelet antibodies. Finally, ultrasonography did not reveal any signs of venous thromboembolic disease and an abdominal evaluation was negative for macroscopic liver or kidney disease.

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Table 1 Summary of laboratory tests in a patient with oxaliplatin-induced hemolytic anemia during adjuvant treatment for resected colon cancer

	Before 11th L-OHP infusion	Day 1 after L-OHP infusion	Day 3	Day 4	Day 24 (hospital discharge)	Follow-up
RBC ($\times 10^6$/mm^3)	3.67	3.43	3.26	2.89	3.06	4.49
Hgb (g/dl)	11.20	10.10	9.9	8.60	9.00	13.60
HCT (%)	34.30	30.5	29.5	25	28.70	40.30
MCV (fl)	93.5	88.9	90.5	88.70	93.80	89.80
PLT ($\times 10^3$/mm^3)	117	25	17	11	204	155
LDH (U/l)	NA	2438	1689	452	NA	NA
Creatinine (mg/dl)	0.83	5.45	7,08	6,46	1.53	1.36
Blood urea nitrogen (mg/dl)	16	121	113	115	21	23
Total bilirubinemia (mg/dl)	1	5.2	1.4	0.8	0.9	0.7
Nonconjugated bilirubinemia (mg/dl)	0.8	3.7	1	0.6	0.7	0.5
AST (IU/l)	26	582	70	9	21	24
ALT (IU/l)	15	173	80	23	20	20

AST, aspartate aminotransferase; ALT, alanine aminotransferase; HCT, hematocrit; Hgb, hemoglobin; LDH, lactate dehydrogenase; L-OHP, oxaliplatin; MCV, mean cell volume; NA, not available; PLT, platelets; RBC, red blood cells.

The clinical picture suggested acute autoimmune hemolytic anemia (AIHA), and therefore the patient underwent plasmapheresis and received methylprednisolone (40 mg/day intravenous), and, during the following 10 days, hemodialysis via a femoral access; no red blood red cell transfusion was necessary. Renal function progressively improved: after transient polyuria, daily diuresis returned to n.v. in 9 days and dialysis was stopped. Blood tests showed stabilized and subsequent improved erythrocyte and platelet counts, and the patient was discharged from hospital after 24 days.

A clinical follow-up examination in June 2006 was negative for signs of relapsed hemolysis or fibrinolysis. The patient recovered well and the chemotherapy has been definitely discontinued.

Discussion

The differential diagnosis in our case concerned the different forms of acquired hemolytic anemia: microangiopathic hemolytic anemia, thrombotic thrombocytopenic purpura and other secondary forms with an infectious etiology. A diagnosis of thrombotic thrombocytopenic purpura had to be considered because of the presence of anemia and thrombocytopenia, but a number of factors excluded this hypothesis in favor of a diagnosis of AIHA: (1) the absence of schistocytes in the peripheral blood smear; (2) the sudden onset of the clinical findings after numerous administrations of oxaliplatin, previously described in the literature; and (3) most importantly, a positive Coombs or direct antiglobulin test, which is almost pathognomonic for a diagnosis of AIHA.

A direct antiglobulin test demonstrates the presence of antibodies on the surface of red blood cells and is the hallmark of autoimmune hemolysis [7]. Renal failure in AIHA may be due to renal tubular damage induced by free hemoglobin, and, although this is not a frequent occurrence during AIHA, we can hypothesize that the rapid appearance of hemolysis and reduced fluid intake for about 24 h led to the complication in this patient [8]. D-dimers are rarely evaluated in the case of AIHA, but we mention the high value encountered in our patient for the sake of completeness. The examination was initially performed as part of a battery of general tests, including those aimed at excluding or suspecting a diagnosis of disseminated intravascular coagulation, such as the coagulation and fibrinogen tests. D-dimer is a product of the digestion of fibrin by plasmin and as its levels increase under various conditions of activated coagulation, the test can only be considered aspecific, even though one study in dogs has shown a correlation between high D-dimer values and AIHA [9].

Associated with anemia, our patient manifested marked thrombocytopenia and the result of the search for antiplatelet antibodies was negative. Our laboratory uses the GTI–PakPlus kit, which is based on a qualitative immunoenzymatic method (enzyme-linked immunosorbent assay) for detecting both anti-HLA class I antibodies and antibodies against platelet-specific antigens: glycoproteins Iib–IIIa, Ib–IX, Ia–IIa and IV. The direct assay for the measurement of platelet-bound antibodies [10] has an estimated sensitivity of 49–66%, an estimated specificity of 78–92% and an estimated positive predictive value of 80–83% [11,12], but a negative test cannot be used to rule out the diagnosis [11,13]. The detection of unbound plasma antibody is less useful; inter-laboratory agreement in the detection of platelet-bound antibody is 55–67%, but the extent of agreement in the detection of plasma antibody is lower [14]. It cannot, therefore, be excluded that the thrombocytopenia developed by the patient within 24 h of the drug infusion may have had an autoimmune pathogenesis.

Oxaliplatin is a water-soluble platinum compound characterized by a diaminocyclohexane platinum carrier ligand. It induces the formation of platinated DNA adducts, thus leading to the inhibition of DNA synthesis and repair, and, finally, apoptosis; with regard to the original platinum compound (cisplatin), the

diaminocyclohexane platinum carrier ligand leads to more effective action on nucleic acid metabolism without increasing general drug toxicity. The currently recognized side effects of oxaliplatin include peripheral neurotoxicity (usually reversible paresthesias and dysesthesias), nausea and vomiting. In comparison with cisplatin or carboplatin, renal toxicity is limited. Furthermore, when used in combination with 5-FU, the usual toxicity associated with 5-FU (mucositis, diarrhea and myelosuppression) is only moderately increased [15,16]. The chemical and biological differences from the other platinum compounds, however, has led to a general underestimate of the adverse effects generally associated with this drug class, mainly hypersensitivity reactions; these reactions themselves ranged from facial flushing or itching to seizures, dyspnea and anaphylaxis. It is known that the increased use of carboplatin led to the observation of hypersensitivity reactions [17]: as the use of carboplatin increased, single centers reported hypersensitivity reactions in the 10.2–19.6% range for adjuvant/first-line and second-line settings, respectively [18,19].

Reports of oxaliplatin-induced hemolytic anemia date to 1999 [2], but only a few cases have been published. As pointed out by Sørbye *et al.* [20], the oxaliplatin-induced reaction may resemble Evans' syndrome, with antibody-mediated destruction of both platelets and erythrocytes. The pathogenesis of the hemolytic anemia remains unknown, but a number of mechanisms have been implicated and there is some suggestion that it may be an immune-mediated process consistent with a type B adverse drug reaction – an adverse effect that is idiosyncratic, unrelated to the pharmacological action of the drug, unpredictable and uncommon [21].

Significantly, all of the hemolytic events have been identified in patients after several treatments, as in the case of carboplatin or cisplatin hypersensivity reactions. Furthermore, adverse reactions (as rhinitis, conjunctivitis, asthma, urticaria, and contact dermatitis) have been reported among refinery workers inhaling complex salts of platinum, thus suggesting that prolonged and repeated exposure to platinum is a risk factor [22]. It is believed that platinum salts act as haptens by binding to serum proteins and repeated exposure to these complexes increases the probability of activating the immune system, thus promoting hypersensitivity reactions [17,22,23]. Similarly, in our case, 10 of the planned 12 treatments induced mild, transient side effects, AIHA developed only during the 11th L-OHP infusion. Only seven reports concerning oxaliplatin-induced hemolytic anemia have been published, but all of them describe the hemolysis and subsequent acute renal failure as late complications after high cumulative doses of oxaliplatin or several cycles of therapy [2–4,20,21,23,24].

Second, and in line with these speculations, the prognosis of the patients affected by oxaliplatin-induced hemolysis is better when an early diagnosis is followed by prompt treatment with steroids or plasmapheresis.

In conclusion, although oxaliplatin remains essential in patients affected by gastrointestinal tumors, the risk of hypersensitity reactions should not to be underestimated, particularly upon repeated dosing. Drug infusions should be closely monitored and all healthcare personnel should be informed of the risk of sudden, potentially lethal reactions. In the case of acute hemolysis, important signs may be transient, intense back pain, scleral jaundice and dark-colored urine. Plasmapheresis combined with intravenous corticosteroids seems to be an efficacious therapeutic approach, possibly followed by hemodialysis in the case of acute renal failure. Finally, we believe that AIHA may occur more frequently than the few published reports would otherwise suggest.

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