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Hemolytic uremic syndrome induced by infusion of oxaliplatin: a case report

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ABSTRACT

Introduction. Oxaliplatin is a third-generation platinum compound with proven antitumor activity in the treatment of colorectal cancer. The occurrence of life-threating hemolitic uremic syndrome has been observed after oxaliplatin therapy. The kind of tumor and treatment modalities seem to influence the onset of hemolitic uremic syndrome.

Methods. The clinical course of the case is reviewed and compared with reports of other similar cases in the literature.

Results. We describe the development of hemolitic uremic syndrome as a result of prolonged oxaliplatin treatment of a colon cancer patient.

Conclusions. Although this rare event requires the concurrence of other unknown factors, it should be considered in a decision-making setting.

Introduction

Oxaliplatin is a third-generation platinum derivative with proven antitumor activity in the treatment of colorectal cancer. The combination of oxaliplatin with 5-fluorouracil and leucovorin has proven efficacy in the adjuvant, first- and second-line setting[1]. Common side effects are cumulative sensory neuropathy, diarrhea, mild myelosuppression and mucositis[2]. Acute onset hemolysis and thrombocytopenia associated with the drug have been rarely reported.

We report a patient with hemolytic uremic syndrome (HUS) that developed after the 17th cycle of oxaliplatin-based chemotherapy.

Case report

A 49-year-old woman without previous major pathologic history had a diagnosis of colorectal cancer with liver metastasis. The patient received as first-line therapy: oxaliplatin, 85 mg/m^2 day 1; folinic acid, 200 mg/m^2: 5-fluorouracil bolus, 400 mg/m^2; 5-fluorouracil, 1200 mg/m^2, 44 h continuous infusion, for 2 consecutive days every 2 weeks (FOLFOX4). The standard 12 cycles were completed in December 2006 with no adverse events and resulted in a marked reduction of the primary tumor and partial regression of the liver metastasis.

On 15/01/2007, the patient underwent removal of the residual primary tumor, right hepatectomy, enucleoresection, followed by radiofrequency ablation of the liver metastases.

In October 2007 owing to progressive omental disease, the patient underwent a second line of chemotherapy including irinotecan (180 mg/m^2 day 1), folinic acid (200 mg/m^2), 5-fluorouracil bolus (400 mg/m^2), 5-fluorouracil (1200 mg/m^2 44 h continuous infusion) for 2 consecutive days every 2 weeks - FOLFIRI. A total of 6 cycles was administered.

Key words: chemotherapy, colorectal cancer, hemolytic uremic syndrome, oxaliplatin.

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In March 2008, the patient was submitted a omentectomy for omental progression of disease. After the second surgery the patient received six course of chemotherapy with FOLFIRI and bevacizumab until November 2008.

In January 2009, the patient was given rechallenge chemotherapy including oxaliplatin for further progression of disease in the lungs and liver and a gradual increase in the marker. Four cycles of chemotherapy were administered without complicactions. At the beginning of the fifth cycle (17th course of oxaliplatin), the patient developed clinical and biochemical abnormalities consistent with the development of HUS: back pain, hematuria, upper gastrointestinal bleeding. Hemolysis was documented by thrombocytopenia (PLTS 33000/L), anemia (Hb 8.7 g/dl), elevated D-dimmers (>40 µg/mL) and LDH (4074 UI/l), indirect bilirubin indices (9.3 mg/dL), severe reduction of haptoglobin (<3 mg/dl) and fibrinogen (<50 mg/dL) and strongly positive Coomb's test. Signs of acute renal failure (creatinine, 3.2 mg/dL; blood urea clearance, 11 ml/min, blood creatinine clearance, 23 ml/min) and moderate hepatic failure (AST 338 IU/l, ALT 109 IU/l, GGT 19 IU/l, INR 7.7) confirmed the diagnosis of HUS.

Chemotherapy was immediately discontinued and emergency treatment was initiated. This entailed: i.v. hydration, loop diuretics, high-dose corticosteroids, and daily frozen plasma infusion.

The hematological and biochemical parameters gradually improved 15 days after the HUS (Hb 8.7 g/dl; platelets 91,000/l; total bilirubin indices, 1.4 mg/dL; fibrinogen, 202 mg/dl; creatinine, 1.6 mg/dl; INR, 1.26) and returned to normal values after one month, when the patient became asymptomatic. After one year, the patient died for disease progression.

Discussion

HUS and thrombotic thrombocytopenic purpura (TTP) share clinical features and severity, leading some to recommend the term "TTP-HUS". Indeed, whereas microangiopathic anemia, thrombocytopenia, hemolysis and neurological abnormalities are common features of TTP and HUS, dominance of high-grade renal impairment is characteristic of HUS[3,4].

In the last few years, life-threatening HUS onset has been reported, in selected patients, as a side effect of chemotherapy. Some conditions seems to favor the drug-associated HUS: adenocarcinoma (especially gastrointestinal), partial-to-complete response of tumor to treatment, non-cardiogenic pulmonary edema, use of mitomycin in the therapuetic regimen[5]. A number of drugs have been implicated as a causal agents of either acute, immune-mediated (clopidogrel, ticlopidine), or cumulative, dose-dependent (mitomycin C >100 cases)[6], gemcitabine (overall incidence 12 of 78,854 cases)[7] HUS. There is no evidence in the scientific literature about a causative role of capecitabine in HUS.

The combination of oxaliplatin with 5-fluorouracil and leucovorin has demonstrated efficacy in the treatment of colorectal cancer in various settings of chemotherapy. The most common adverse effects are reversible peripheral neuropathy, diarrhea and mild neutropenia. Occurrence of severe HUS has also been reported after oxaliplatin therapy. Due to the small number of events reported (13 cases in the literature from 1999-2009)[8], oxaliplatin-induced HUS has received little attention. The case described here may provide some hints as to whether the kind of cancer and the drug administration schedule may favor HUS development.

Three mechanisms have been considered for the pathogenesis of hemolysis with thrombocytopenia associated with oxaliplatin-based chemotherapy: 1) antibody-mediated destruction of platelets and erytrocytes, 2) microangiopathic hemolytic anemia due to drug-induced TTP, 3) microangiopathic hemolytic anemia due to disseminated intravascular coagulation[9]. Hemolysis derived from the adsorption of oxaliplatin (immune complexes) on the surface of red blood cells has also been considered a probable cause or contributing factor (such a phenomenon is invariably associated with a positive direct Coomb's reaction)[10,11].

Oxaliplatin-induced HUS reported in literature occurred in patients receiving far more administrations of oxaliplatin than the foreseen standard schedule[12-20]. Our patient, after the first positive response to the scheduled 12 oxaliplatin administrations, also received additional five doses to control tumor relapse resistant to other drugs. Together, these data strongly support the concept that prolongation of oxaliplatin therapy favors HUS development. Drug-induced sensitization seems therefore to be the most likely mechanism involved in the pathogenesis of HUS. Colon cancer is more prone to HUS. In ours as well as in previous reports, most patients who showed oxaliplatin-induced HUS were women with colorectal cancer[8]. It is therefore difficult to assess the relative pertinence of the tumor *versus* the drug in the development of HUS. HUS that developed after mitomycin C treatment showed a prevalence of colon cancer, circumstantial evidence of a combined effect of the growing tumor and chemotherapy.

The treatment remains controversial. The obvious action is discontinuation of the offending agent, accompanied by prompt supportive care. The latter must include: hydration, high-dose corticosteroids, loop diuretics and plasma supply. As for the latter, fresh frozen plasma infusion or plasma exchange are both employed[21-23], although the superiority of either method has not been proven. Alternative therapies do not confer additional benefit but increase risk[24]. The case reported here was managed with fresh frozen plasma infusion.

Conclusions

We report a case of HUS that developed in a colon cancer patient during oxaliplatin treatment. The present report confirms previous data of a close association between HUS and prolonged oxaliplatin administration. The establishment of an immune memory, tumor histology and other unknown factors seem to be responsible for HUS, whose development has to be taken into account in the decision-making process.

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