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SHORT COMMUNICATION

Oxaliplatin-induced immune mediated thrombocytopenia

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Abstract Oxaliplatin is a third generation platinum compound used in patients with advanced colorectal carcinoma. Recently, the mechanism of a rare drug-induced immune thrombocytopenia in patients receiving oxaliplatin has been described. This complication is caused by oxaliplatin-dependent antibodies directed against platelet surface glycoproteins, and is unrelated to myelosuppression. In this report, we describe two patients who developed thrombocytopenia immediately soon after receiving oxaliplatin. Sensitization presumably had occurred after receiving oxaliplatin during preceding courses of multiagent chemotherapy that included oxaliplatin.

Keywords Oxaliplatin · Immune · Thrombocytopenia

Background

Oxaliplatin is a third generation platinum compound with significant activity as first and second line therapy in patients with advanced colorectal carcinoma [1–3]. Unlike the older member of its family cisplatin, oxaliplatin has little renal or ototoxicity. Recent literature has described the mechanism of a rare drug-induced immune thrombocytopenia in patients receiving oxaliplatin as being caused by oxaliplatin-dependent antibodies directed against glycoprotein IIb/IIIa, and unrelated to myelosuppression [4]. In this report, we describe two cases of immediate-onset severe thrombocytopenia secondary to oxaliplatin.

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Case reports

Patient 1

A 74-year-old woman, with a history of metastatic rectal carcinoma to the liver and lungs, received 12 cycles of FOLFOX-4 (oxaliplatin, leucovorin and infusional 5-fluorouracil) with complete resolution of the primary tumor and excellent response in the liver. After being off treatment for nine months, she developed progressive disease and was restarted on FOLFOX-4 plus bevacizumab. While receiving oxaliplatin infusion during the fifth cycle of chemotherapy, the patient began bleeding from her catheter site and developed petechiae over her body. Laboratory examination showed a decrease in her platelet count from 113,000/μL in the morning prior to her chemotherapy, to 6,000/μL. Platelet antibodies were positive for anti-platelet circulating IgG as well as IgM and negative for IgA. Peripheral blood smear was unremarkable except for rare platelets. Hemoglobin, reticulocyte and granulocyte counts, prothrombin time and fibrinogen were within normal ranges for the patient. She was hospitalized and transfused platelets, subsequently her platelet count recovered to 90,000/uL over one week. Due to the rapid fall of platelets from 113,000 to 6,000/μL within hours of initiation of infusion of oxaliplatin the diagnosis of acute immune-mediated thrombocytopenia due to oxaliplatin was made. Therefore, chemotherapy was changed to irinotecan and

cetuximab, and is presently doing well, without recurrence of thrombocytopenia following subsequent chemotherapy administrations.

Patient 2

An 83-year-old woman with metastatic rectal carcinoma to the liver had previously completed 10 cycles of FOLFOX-4 (oxaliplatin, leucovorin and infusional 5-fluorouracil). Her treatment had been discontinued due to fatigue, poor functional state and general intolerance. Her therapy was subsequently restarted with irinotecan and cetuximab due to progressive disease. Her disease continued to progress on this last regimen she was restarted on FOLFOX-4 plus bevacizumab. After 1 hour of her second dose of oxaliplatin, the patient developed acute mental status changes, nausea, diarrhea and significant thrombocytopenia. Laboratory examination was significant for platelets of 41,000/μL which dropped from 160,000/μL on the morning of receiving chemotherapy. All other counts remained stable with WBC of 3.0×10^3/μL, Hemoglobin 13.3 g/dL, Hematocrit 39%. Haptoglobin, fibrinogen, bilirubin (total and direct) and coagulation studies were all normal. Peripheral smear revealed rare platelets and no schistocytes. The patient was admitted for stabilization and the thrombocytopenia was corrected with platelet transfusions. Subsequently the patient's regimen was changed to bevacizumab with 5-FU and leucovorin and her platelet counts continued to remain stable.

Discussion

Oxaliplatin is approved by the Food and Drug Administration (FDA) as first and second line treatment for use in combination with infusional 5-Fluorouracil (5FU) and Lekovorin (LV) for patients with metastatic carcinoma of the colon or rectum [5]. Toxicities are similar to that of other platinum based compounds and include peripheral neuropathy, mild bone marrow suppression and gastrointestinal side effects. However, with widespread use of this drug, more rare complications, like thrombocytopenia related to oxaliplatin, have come to light.

Recent reports have showed acute thrombocytopenia with or without acute hemolysis, during or immediately after infusion of oxaliplatin based chemotherapy. Such precipitous drops in platelets cannot be attributed to just bone marrow suppression or marrow replacement by tumor, and thus suggest an underlying platelet destructive process.

Curtis et al. [4] observed acute onset thrombocytopenia in two patients during the 11th and 17th cycle of oxaliplatin and showed the presence of high titers of IgG antibody that reacted with normal platelets in the presence of soluble oxaliplatin. Serum from the patients in this study did not develop a reaction to carboplatin suggesting specificity of this phenomenon to oxaliplatin. Also the serum from the two patients failed to react in the presence or absence of oxaliplatin with platelets from a patient with type I Glanzmann thrombasthenia lacking detectable GPIIb/IIIa. Telaghani et al. [6] defined a patient with immune mediated pancytopenia during the 17th cycle and demonstrated oxaliplatin dependent antibodies to red blood cells, platelets and neutrophils. In another case, the authors reported thrombocytopenia without any demonstrable hemolytic anemia during the 19th cycle of oxaliplatin within 4 h of cessation of infusion [7]. Similarly Koutras et al. [8] reported a case of acute thrombocytopenia, bleeding, and hemolysis during the 14th cycle of chemotherapy with oxaliplatin and suggested a drug induced thrombocytopenia where antibodies react with the absorbed antigen on the surface of platelets and lead to their destruction.

These reactions are believed to be related to drug induced immune thrombocytopenia (DIIT) in which destruction is caused by immunoglobulins that recognize specific platelet membrane glycoproteins in the presence of a sensitizing drug. Drug induced antibodies specific for platelets are not able to recognize cells pretreated with the drug, instead only react in the presence of the soluble drug. Circulating antibodies to platelets were demonstrated in one of our two patients, which is seen in immune and drug induced thrombocytopenia.

The question of whether or not it is safe to readminister oxaliplatin after developing DIIT will become even more important with the increasing use of oxaliplatin based chemotherapy. However, it has been suggested that drug sensitivity usually persists indefinitely in patients with drug induced immune thrombocytopenia, and readministering the same drug at a later date can be hazardous [4]. It should be noted that our patients developed symptoms within hours of insfusion after safely being initially exposed to oxaliplatin 8–9 months prior.

Drug-induced immune thrombocytopenia should be considered in patients on chemotherapy who have a sudden, isolated drop in platelet levels not explainable by myelosuppresion. The demonstration of circulating antiplatelet IgG and IgM in patient 1, in light of the recent literature, furthers supports the emerging concept that oxaliplatin can cause immune-mediated thrombocytopenia on rare occasions.

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