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Oxaliplatin induced acute immune-mediated thrombocytopenia; a case report

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ABSTRACT

Oxaliplatin is a third-generation platinum anti-neoplastic agent, which is used in the treatment of colorectal, gastric, and biliary tract cancers with combination other chemotherapy drugs. In rare cases, thrombocytopenia may occur suddenly in approximately 24 hours due to immune-mediated reactions. This reaction is usually seen after long term usage of oxaliplatin-based chemotherapy. Here, we present our case of immune-mediated thrombocytopenia associated with oxaliplatin.

A 56 years old man who had stage IV rectum cancer with liver metastasis, had palliative surgery due to bowel obstruction after initial diagnostic approach. After failure of first line treatment, mFOLFOX6 plus Cetuximab (Cetuximab: 500mg/m² on day 1, Oxaliplatin: 85 mg/m² day 1, Leucovorin (LV): 400 mg/m² day 1, 5-FU 400 mg/m² IV bolus on day 1 followed by 2400 mg/m² on day 1 infused over 46 hours every two weeks) regimen was started. Before the 21st cycle of oxaliplatin plus cetuximab regimen, the patient had normal thrombocyte, haemoglobin and neutrophil count. Approximately 8 hours after the chemotherapy patient had been taken to the emergency service with petechia, vigorous gastrointestinal and nasal bleeding. The thrombocyte levels were 3000 at μ l. The patient was given methylprednisolone for three days. The thrombocyte levels recover quickly in 24 hours. After this reaction, oxaliplatin stopped and the chemotherapy was changed to capecitabine plus cetuximab regimen.

In conclusion, oxaliplatin induced immune-mediated thrombocytopenia is a rare side effect but a life threatening complication. A physician who uses oxaliplatin as a treatment option should keep in mind the possibility immune-mediated thrombocytopenia which may cause life-threatening bleeding. Especially the long term use of oxaliplatin (median >10 cycles) may alert the physician for immune-mediated adverse effects.

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1. Introduction

Oxaliplatin is a third-generation platinum anti-neoplastic agent, which is used in the treatment of colorectal, gastric, and biliary tract cancers in combination with other chemotherapy drugs. The most common side effects of this agent is peripheral neuropathy, myelosuppression, nausea, and vomiting. In chemotherapy regimens with oxaliplatin, up to 70% of patients had various grades of thrombocytopenia as an adverse effect.^{1,9,10} In oxaliplatin monotherapy, thrombocytopenia may be seen about 30% and it is usually moderate, self-limited, and related to myelosuppression.¹ Only 3–4% of patients have grade 3–4 myelosuppression related

thrombocytopenia with life-threatening bleeding.^{1,9,10}

In rare cases, thrombocytopenia may occur suddenly in approximately 24 hours due to immune-mediated reactions.² This potentially life-threatening side effect occurs by Type II hypersensitivity reaction. Antibodies against oxaliplatin neoepitope can affect red blood cells, platelets, leucocytes and the other blood glycoproteins.¹³ This reaction is usually seen after long term usage of oxaliplatin-based chemotherapy.

Clinical presentation of this drug induced immune thrombocytopenia is quite varied. Patients usually complain of isolated thrombocytopenia related symptoms with or without haemolytic anemia, leucopenia, impairment of renal and hepatic functions, and skin reactions.^{2–8}

Here we present a case of immune-mediated thrombocytopenia associated with oxaliplatin.

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2. Case

A 56 years old man who had stage IV rectum cancer with liver metastasis, had palliative surgery due to bowel obstruction after initial diagnostic approach. The pathological specimen of the patient evaluated as K-Ras wild type. The patient was given neo-adjuvant FOLFIRI plus Bevacizumab (Bevacizumab: 5 mg/kg on day 1, irinotecan: 180 mg/m² on day 1, leucovorin: 400 mg/m² on day 1, 5-FU 400 mg/m² IV bolus on day 1 followed by 2400 mg/m² on day 1 infused over 46 hours every two weeks) regimen for the conversion of the border-line resectable liver metastases. After the 6 cycles of chemotherapy (3 months), partial response was seen radiologically. The patient was undergone surgery for the metastasectomy of the liver metastases, but R₀ resection cannot be achieved. So FOLFIRI plus Bevacizumab regimen continued for 6 cycles more. Progression was detected radiologically after 12 cycles of FOLFIRI plus Bevacizumab treatment. Second-line mFOLFOX6 plus Cetuximab (Cetuximab: 500mg/m² on day 1, Oxaliplatin: 85 mg/m² day 1, Leucovorin (LV): 400 mg/m² day 1, 5-FU 400 mg/m² IV bolus on day 1 followed by 2400 mg/m² on day 1 infused over 46 hours every two weeks) regimen was initiated. After 12 cycles (6 months), partial response achieved. Reduction in marker levels, tumour shrinkage in radiological studies and improvement in clinical performance status was noted. As the maintenance therapy, oxaliplatin and cetuximab regimen was continued for 8 cycles. Before the 21st cycle of oxaliplatin plus cetuximab regimen, the patient had normal thrombocyte, haemoglobin and neutrophile count. Approximately 8 hours after the chemotherapy patient had been taken to the emergency service with petechia, vigorous gastrointestinal and nasal bleeding. (Fig. 2–3) No allergic reactions were seen in the physical examination like urticaria, angioedema, wheezing or rushes. The thrombocyte levels were 3000 at μ l. The patient was hospitalized for gastrointestinal bleeding and received 10 random thrombocyte transfusions immediately. He was given 60 mg methylprednisolone for three days. On the 24th hour of oxaliplatin infusion, the thrombocyte levels raised to 38000 at μ l. In the second day the thrombocyte levels stabilized and gastrointestinal bleeding stopped. (Fig. 1) Anti-thrombocyte antibodies could not perform because of test unavailability. The fast reduction in thrombocyte count in 12 hours time was considered for oxaliplatin associated immune-mediated thrombocytopenia. After this reaction, oxaliplatin stopped and the chemotherapy was changed to capecitabine plus cetuximab regimen. The thrombocyte levels were

normal with this chemotherapy regimen. No adverse reaction was noted.

3. Discussion

Myelosuppression is the main cause of thrombocytopenia related to oxaliplatin, which represents generally moderate and asymptomatic thrombocytopenia. In some patients, hepatic sinusoid damage by oxaliplatin leads to portal hypertension and the splenic sequestration of platelets can be resulted thrombocytopenia. Immune-mediated mechanism is the third reason of thrombocytopenia which is quite rarely occurs during oxaliplatin infusion or soon after ¹¹. This rare side affect occurs by Type II hypersensitivity reactions when antibodies (IgG and/or IgM) recognize surface antigens on host cells and mediate cell lysis via complement and phagocytic cells. Especially, glycoprotein IIb/IIIa or other platelet glycoproteins are targeted by the production of oxaliplatin-dependent specific antibodies. But, mechanism of this drug induced toxicity is not yet clearly understood.

The findings from the clinical evaluation will usually be sufficient for the diagnosis of oxaliplatin induced thrombocytopenia without need for specific antibodies. Sudden onset thrombocytopenia (usually occurs in 24 hours after chemotherapy) and thrombocytopenia related petechia, purpura, and gastrointestinal bleedings are the main clinical findings. Haemolytic anemia, leucopenia, allergic reactions, and or impairment of renal and liver functions were described previously in patients receiving oxaliplatin-based chemotherapy after a prolonged exposure ^{2–8, 12–13}. The treatment has to initiate rapidly to avoid complications, because fatal cases have been reported in published studies. The treatment includes supportive care and discontinuation of drug. Steroids and intravenous immunoglobulin (IVIG) might be an option for immune mediated thrombocytopenia ¹².

Due to our best knowledge, there are two published review articles in the literature ^{12–13}.

The review article published by Erdem et al. in April 2016 ¹². Clinical features of 42 cases immune mediated thrombocytopenia due to oxaliplatin use presented. One of the patients was from their institution and the other 41 cases were found in Pubmed screening. According to this review, most of patients were female (54.7%), the age of patients were differ from 38 to 83 years and the emerge of the reaction changed from sudden onset to 24 hours. The infusion numbers of oxaliplatin differed second to thirtieth cycle (average 15

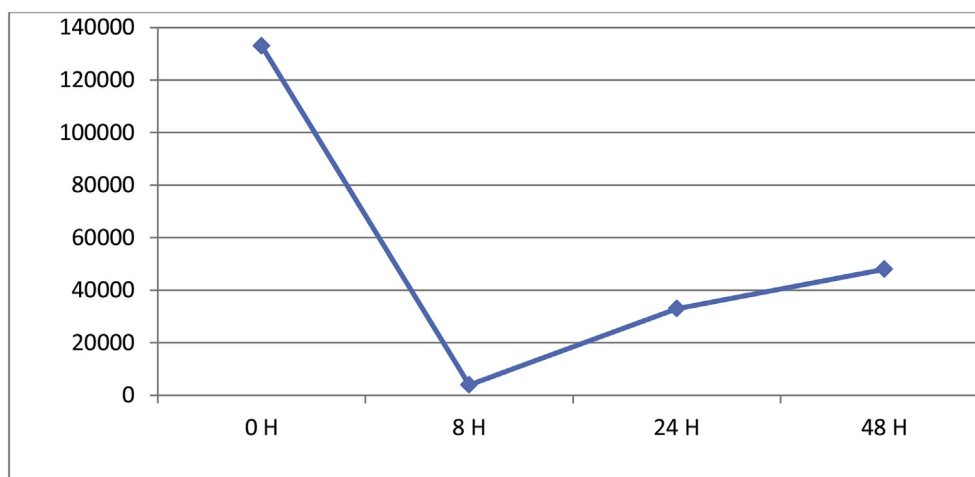


Fig. 1. The course of Thrombocyte counts of the patient on the days of chemotherapy and hospitalization.

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