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Title

Oxaliplatin immune-mediated thrombocytopenia: is there a role for pre-medication or desensitization?

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Data availability statement

The data that supports the findings of this study are available in the supplementary material of this article.

What is already known about the subject?

Immune-mediated thrombocytopenia is a rare and potentially life-threatening adverse effect of several drugs, including the chemotherapy drug oxaliplatin.

Treatment under desensitization protocol or attempts for re-challenge after prolonged withdrawal of oxaliplatin have not been described.

Our main goal was to describe this adverse effect and to present our experience in treating patients who experienced recurrence despite different methods of prevention.

What this study adds?

Due to the rarity and severity of this adverse effect, it is not well known and described.

Our case series presents three cases of oxaliplatin immune-mediated thrombocytopenia and how despite prolonged withdrawal of the drug or using a desensitization protocol – patients who previously experienced this adverse effect are still at high risk of recurrence and rechallenge should not be attempted.

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Oxaliplatin immune-mediated thrombocytopenia: is there a role for pre-medication or desensitization?

Abstract

Oxaliplatin is a common chemotherapy agent that is used in the treatment of multiple solid malignancies. Immune-mediated thrombocytopenia is a rare and potentially life-threatening adverse effect of oxaliplatin that is characterized by severe thrombocytopenia which may be accompanied by overt bleeding.

This adverse effect is most likely mediated via anti-platelet antibodies that become reactive in the presence of oxaliplatin. Due to its rarity and severity, information is scarce regarding the effect of desensitization or attempts at rechallenge after prolonged withdrawal of oxaliplatin.

This short report describes three cases of oxaliplatin immune-mediated thrombocytopenia, including a case occurring under desensitization protocol and a case of recurrence after a prolonged withdrawal. All three patients are female, have prolonged exposures to oxaliplatin and were all treated for metastatic colorectal cancer.

Physicians should be aware of oxaliplatin immune-mediated thrombocytopenia as symptoms may appear rapidly. Oxaliplatin should be permanently discontinued for patients experiencing this adverse effect, as recurrence is highly likely even in the setting of desensitization.

Introduction

Thrombocytopenia is a common side effect of various chemotherapeutic drugs, usually as a result of direct myelosuppression. Oxaliplatin, a platinum derivative indicated in multiple types of cancers, is known to cause thrombocytopenia in approximately 30% of patients when used as a single agent, and in up to 77% of patients when it is administered in combination with other myelosuppressive drugs, such as 5-fluorouracil¹. Grade 3/4 thrombocytopenia is rare and can usually be averted by decreasing the dose of oxaliplatin, allowing for continuity of treatment.

Despite the rarity of oxaliplatin immune-mediated thrombocytopenia, it is a potentially fatal adverse effect of oxaliplatin that is characterized by acute onset of severe thrombocytopenia (platelets usually less than 20K/ul). Previous case reports suggested that some patients who developed immune-mediated thrombocytopenia share common characteristics such as female gender, multiple oxaliplatin exposures and previous hypersensitivity reactions².

Due to the rarity and severity of this adverse effect, data is scarce regarding its occurrence under pre-medication, prolonged drug cessation or under desensitization protocols. However, this information is critical since cessation of oxaliplatin in a responding patient has potential prognostic implications. We here present three patients with oxaliplatin immune-mediated thrombocytopenia, including a case of thrombocytopenia recurrence following re-

challenge with oxaliplatin after a prolonged withdrawal of the drug and a case of thrombocytopenia that occurred under desensitization protocol.

Keywords: chemotherapy; drug allergy; patient safety; medical oncology;

Methods

We describe three cases of oxaliplatin immune-mediated thrombocytopenia that occurred in the years 2019 and 2020 at the Department of Oncology, Sheba Medical Center, Tel HaShomer, Israel.

Patient factors such as age, gender, treatment protocols, pre-medication regimens, presence of liver metastases and number of previous oxaliplatin treatments were collected. Any pre-medications given prior to treatment with oxaliplatin were recorded. Laboratory tests for each patient include a complete blood count (CBC) and a full chemistry workup including LDH and bilirubin.

Reaction characteristics such as time to appearance of symptoms, the presence of fever and overt bleeding are described for each patient as well as treatment with steroids, platelets, and the need for hospitalization.

Results

Case 1

The first case is a 45-year-old female with metastatic CRC, who was admitted to the oncologic day care unit for her biweekly 18th treatment with oxaliplatin and capecitabine (as part of the XELOX protocol) together with bevacizumab. She was regularly pre-medicated with intravenous 12mg of promethazine and 100mg of hydrocortisone due to chills and fever following her 2nd treatment. CBC from a day prior to her admission was unremarkable with a platelet count of 207K/uL. Shortly after receiving bevacizumab and oxaliplatin, the patient developed a fever of 40.0°C and a tachycardia of 133 bpm. She was immediately treated with antipyretics.

Immediately following the onset of fever, the patient reported gross hematuria and multiple petechiae. Laboratory tests revealed thrombocytopenia of 14K/uL. Hemoglobin and ANC were within normal ranges. Markers of hemolysis were also present, with bilirubin levels of 4.53mg/dL (mostly direct bilirubin), LDH of 826IU/L (normal range 100-260) and an extremely low haptoglobin of < 7.5mg/dL (normal range, 30-200). Coagulation panel was unremarkable. A direct antiglobulin test (DAT) was positive. Blood cultures and a respiratory virus panel were negative. The patient was hospitalized and treated with steroids with a gradual recovery of her platelet counts within days. Further treatment was changed to irinotecan and 5-fluorouracil without recurrence of thrombocytopenia.

Sixteen months later, due to unbearable side effects of irinotecan, her treating physician resumed treatment with capecitabine and oxaliplatin (XELOX), with no adverse events during the first two cycles of treatment. However, immediately following her third cycle, the patient reported petechiae and gross hematuria. Platelet count decreased to 16K/uL from 163K/uL two days prior. Haptoglobin again decreased to < 7.38mg/dL. She was treated with

steroids throughout a whole week with gradual elevation of her platelet count. Treatment with oxaliplatin was permanently discontinued.

Case 2

The second patient, a 71-year-old female with metastatic CRC developed fever of 38.3 Celsius concurrent with mucosal bleeding and epistaxis within 12 hours after her 16th treatment cycle with oxaliplatin, 5-fluorouracil and cetuximab. Her platelet count decreased to 4K/uL from 184/uL two days prior. The patient also experienced mild pruritus during her treatment, which was treated with hydrocortisone 100mg IV and a brief interruption of the infusion. The patient was hospitalized and treated with steroids and platelet infusions. Treatment with oxaliplatin was permanently discontinued.

Case 3

The third patient, a 57-year-old female with metastatic CRC was treated with oxaliplatin given in a desensitization protocol due to previous hypersensitivity reaction of dyspnea and desaturations. Skin testing for immediate hypersensitivity to oxaliplatin were negative. She received pre-medication with prednisone 40mg PO and loratadine 20mg prior to beginning the oxaliplatin desensitization regimen. During her desensitization regimen, she reported the appearance of a non-petechial rash and pruritus which was treated with promethazine 25mg IV and a brief interruption of the treatment protocol. Less than 10 hours later, she developed a petechial rash with a platelet count of 32K/uL (down from 117K/uL three days prior). LDH and bilirubin were also elevated, but similar to her previous laboratory values as she had disseminated liver metastasis. Treatment with oxaliplatin was permanently discontinued. We have summarized all details regarding these three patients in table S1 (see additional file – S1).

Discussion

Thrombocytopenia is a well-known adverse effect of platinum compounds, mainly due to its cytotoxic effect on megakaryocytes³. Oxaliplatin, a platinum compound, is one of the most common cytotoxic drugs used in cancers of the gastrointestinal system. Onset of thrombocytopenia as a result of bone marrow suppression is usually within few days of oxaliplatin exposure, reaching a nadir about 10 days following treatment. Overt bleeding is uncommon, as thrombocytopenia is usually mild³.

Hypersensitivity reactions to oxaliplatin are immune-mediated phenomena that include dyspnea, urticaria, pruritus, and rarely hypotension, bronchospasm and death⁴. According to FDA labeling, grades 3 and 4 hypersensitivity reactions occur in approximately 2-3% of patients with CRC treated with oxaliplatin¹. Mild hypersensitivity reactions can sometimes be prevented using a desensitization regimen, allowing patients to continue treatment with oxaliplatin. Infusion reactions may present similarly to hypersensitivity reactions, but do not have an underlying immunologic mechanism. Infusion reactions to oxaliplatin have been documented and can potentially be treated via prolongation of infusion time or pre-medication.

Oxaliplatin immune-mediated thrombocytopenia is a rare and potentially life-threatening adverse effect characterized by acute onset of severe thrombocytopenia (platelet count under 50K/microL), usually within a few hours following exposure to oxaliplatin⁵⁻⁷. Patients may present with concurrent auto-immune hemolytic anemia (Evan's syndrome), sometimes manifesting as back pain during oxaliplatin infusion². Several risk factors for developing oxaliplatin immune-mediated thrombocytopenia have been identified, including female gender and multiple exposures to oxaliplatin (usually over 12 cycles, regardless of the doses involved)⁸. Of note, some reports have suggested that previous hypersensitivity reactions to oxaliplatin increases the risk of developing oxaliplatin immune-mediated thrombocytopenia². In our report - all three patients share these risk factors. All three patients also experienced a certain previous hypersensitivity reaction to oxaliplatin at some point.

Drug-related immune thrombocytopenia with or without autoimmune hemolytic anemia is classified as type II hypersensitivity reaction, occurring within hours to days following exposure to various compounds⁹. The reaction described in the 1st patient is remarkable in terms of the extremely rapid onset of symptoms following exposure to oxaliplatin, with bleeding appearing less than an hour following treatment with oxaliplatin. Diagnosis of drug-related immune-thrombocytopenia is often clinical and is based mostly upon the clinical presentation in combination with suggestive blood counts. Confirmation of the implicated antibodies can be confirmed via serologic testing, but these are not routinely performed in most medical centers. This is of importance when the offending drug is not easily isolated, or when multiple drugs are suspected as causing the reaction.

The mechanism behind oxaliplatin immune-mediated thrombocytopenia is most probably due to specific antibodies against platelet glycoproteins that acquire specificity to the platelet epitope in the presence of oxaliplatin¹⁰. These antibodies gradually become undetectable when the offending drug is not used. However, when a patient with a past history of drug-related immune-thrombocytopenia is re-exposed to the offending drug, multiple doses might be needed in order to increase the antibody titer required to induce thrombocytopenia. To the best of our knowledge, other chemotherapy agents often given in conjunction with oxaliplatin, such as irinotecan and 5-fluorouracil, do not seem to cross-react with these antibodies, however – these drugs have also been shown to induce immune-related thrombocytopenia. Patients who are treated with an oxaliplatin-containing regimen might develop multiple antibodies against several medications, all of which are able to induce drug-related immune-thrombocytopenia¹¹.

There are no established guidelines for the treatment of patients with immune-mediated thrombocytopenia due to oxaliplatin exposure. Corticosteroids are sometimes used in an effort to suppress the immune response, but there are no established studies to support the use of steroids in this rare setting. Adequate hematological support with platelet transfusions and other blood products is sometimes required for patients with severe thrombocytopenia or bleeding. Plasmapheresis and dialysis for severe case of thrombocytopenia and hemolytic anemia have also been described⁵.

There are no guidelines when considering re-exposure to oxaliplatin in patients experiencing oxaliplatin immune-mediated thrombocytopenia. Patients developing this rare adverse effect are often advised to discontinue oxaliplatin due to high expected risk of recurrence of this potentially fatal complication. However, as oxaliplatin is extensively used in treatment of various malignancies and specifically CRC, its discontinuation in responsive patients may negatively impact oncological outcomes, thus clinicians may be inclined to attempt an oxaliplatin re-challenge, with pre-medication or even desensitization.

To our knowledge, ours is the first documented cases of re-challenge with oxaliplatin following a prolonged drug withdrawal or under a desensitization regimen. The first patient described herein was re-treated with oxaliplatin approximately a year after her initial episode, resulting in recurrence of immune-mediated thrombocytopenia during her third re-treatment cycle. As long-term immune memory is most likely involved in maintenance of anti-platelet antibodies, this type of immune reaction is prone to recur. Unlike other hypersensitivity reactions to oxaliplatin, our experience with the patients described above indicates that immune-mediated thrombocytopenia cannot be overcome with desensitization regimens and that re-challenge is not recommended, even following a prolonged 'oxaliplatin-free period' and with co-administration of pre-medication.

In conclusion, oxaliplatin immune-mediated thrombocytopenia is a rare adverse effect occurring more commonly in female patients with metastatic CRC exposed to multiple doses of oxaliplatin. Prompt identification of these patients is critical, as fatal cases have been described. Patients often require close monitoring of their blood counts and adequate supplementation of thrombocytes and other blood products. Cross-reactivity of these antibodies with other platinum derivatives is unknown, but treatment with other chemotherapy agents appears to be safe. Information is scarce regarding re-challenge with oxaliplatin, but as can be implicated from the patients described herein – re-challenge or desensitization are not recommended as subsequent reactions can be expected.

List of abbreviations

CRC – colorectal cancer

WBC – White blood count

ANC – Absolute neutrophil count

AST - Aspartate transaminase

ALT - Alanine transaminase

LDH - Lactate dehydrogenase

PT – Prothrombin time

PTT - Partial thromboplastin time

hMPRV - Human metapneumovirus

RSV - Respiratory syncytial virus

ANCA – Antineutrophil cytoplasmic antibodies

DAT - Direct Antiglobulin Test

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Author Contribution

Einat Shmueli supervised and conceived the report. Gal Strauss and Ben Boursi collected the data and wrote the paper. Noa Markovits, Ofer Margalit and Naama Halpern provided review and editing of the paper.

Table S1 – patient characteristics

Demographics			Background						Reaction			Labs				Treatment			
Patient	Age	Gender	Cancer type	Liver metastasis	Oxaliplatin infusion #	Treatment protocol	Previous reactions	Premedication	Timing to onset of symptoms	Fever	Bleeding	Platelet count prior to treatment	Nadir of platelet count	Maximal LDH	Maximal Bilirubin	Steroids	Platelet infusion	Hospitalization	Outcome
#1	46	F	Metastatic CRC	No	#21	XELOX	Fever, chills	Hydrocortisone Promethazine Slow infusion rate	<1 Hour	Yes	Yes	163K/uL	9K	920IU/l	4.54mg/dL	Yes	Yes	Yes	Recovery
#2	71	F	Metastatic CRC	No	#16	FOLFOX + Cetuximab	Pruritus	Hydrocortisone during treatment	12 Hours	Yes	Yes	184K/uL	4K	340IU/l	0.71mg/dL	Yes	Yes	Yes	Recovery
#3	57	F	Metastatic CRC	Yes	#15	FOLFOX	Dyspnea, desaturation	Desensitization + Prednisone + Loratadine	12 Hours	No	Yes	117K/uL	32K	681IU/l	3.98mg/dL	Yes	No	Yes	Recovery