Case Report

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Cross-allergic reactions between etoposide and penicillin in autologous bone marrow transplant patient

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Abstract:

Etoposide is a chemotherapeutic agent that belongs to the podophyllotoxin drug class. Etoposide is used in treating many types of cancers including blood cancers. However, hypersensitivity reactions to etoposide and other chemotherapeutic agents are common. A 29-year-old female was admitted to the bone marrow transplant center for autologous hematopoietic stem cell transplantation. She was previously diagnosed with Hodgkin's lymphoma. The Lomustine, Etoposide, Cytarabine and Melphalan, (LEAM) protocol has been prescribed as a conditioning regimen before stem cell transplantation for this patient. On the 4th day of LEAM protocol, after the last day of the etoposide dose, the patient develops a severe allergic reaction to etoposide. After investigation, we found that the patient was allergic to penicillin which also appeared when the patient takes piperacillin + tazobactam. The possibility of cross-allergic reactions between etoposide and penicillin is unknown. The cross-allergic reactions between etoposide and penicillin are not reported in previous studies.

Keywords:

Allergic reaction, anticancer, etoposide, hematopoietic transplantation, penicillin allergy

Introduction

The bone marrow transplantation center has been established more than 70 years ago.[1] The Iraqi bone marrow transplant center, in medical city, has been founded in 2002. This center provides treatments to different hematological conditions such as Hodgkin's lymphoma (HL), non-HL, and acute myeloid leukemia.[2]

In general Bone marrow transplantation (BMT) is divided into two main types: autologous and allogeneic according to the source of stem cells.[3] In autologous BMT, the source of cells is the patient itself, while the source of stem cells in allogeneic BMT is from a donor other than the patient.[3] BMT is essential once high-dose chemotherapeutic agents are used in the treatment of many types of malignant diseases such as HL.[3]

HL is a rare and curable type of hematological malignancy. Many cases that relapsed after treatment with first-line chemotherapy well respond to autologous hematopoietic stem cell transplantation.[4]

Different chemotherapy protocols have been used as conditioning treatments before autologous hematopoietic stem cell transplantation. One of the most commonly used protocols is LEAM. LEAM consists of lomustine, etoposide, cytarabine, and melphalan.[5]

Etoposide is a cytotoxic drug that induces its effects by inhibiting topoisomerase enzymes.[6] Etoposide has been used in the treatment of different types of cancers including HL.[7] The major adverse effects of etoposide are myelosuppression and reduction in white blood cell count.[7]

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Other less toxic adverse effects of etoposide include alopecia, neural toxicity, mucositis, diarrhea, and bronchospasm.[7]

The Food and Drug Administration approved using lomustine for different types of cancer including HL.[8] Lomustine has been used with other chemotherapeutic agents in the conditioning regimens before stem cell transplantation.[5] Nitrosourea drug class which includes lomustine induces its effect by DNA alkylating.[5]

Cytarabine, antimetabolite, is a part of the LEAM protocol.[5] Like other chemotherapies, cytarabine has many adverse effects including gastrointestinal upset, nausea, vomiting, neurotoxicity, and myelosuppression. Furthermore, some people suffered from pulmonary edema after high doses of cytarabine. Reversible corneal complications are frequently reported with high-dose cytarabine administration.[9]

The last drug in LEAM protocol is melphalan. Melphalan is an alkylating agent from the nitrogen mustard chemotherapy class. Melphalan can be administered orally or parenterally. Adverse effects of melphalan include nausea, vomiting, mucositis, and veno-occlusive disease.[10]

Hypersensitivity reactions to drugs are common. There are different types of hypersensitivity reactions to several drugs such as chemotherapy and antibiotics. The main cause of these reactions is not well understood. However, the main mechanism of hypersensitivity reactions is antigen-antibody interaction. The majority of these reactions occur during drug administration, while others may appear after drug administration has been concluded. Hypersensitivity reactions may also cross over different drug classes. Some of these reactions are mild such as rash and itching, while others are considered severe reactions such as hypotension, bronchospasm, dyspnea, alternation of pulse rate, and hyperthermia.[11]

Piperacillin and tazobactam combination (Tazocin) is the first-line empirical antibiotic in patients suffering from neutropenic fever.[12] This broad-spectrum antibiotic is from the penicillin drugs family. A hypersensitivity reaction to Tazocin has been confirmed in several studies.[13] Some of these reactions appear immediately, while others have delayed onset.[14]

Case Study

A 26-year-old female was previously diagnosed with HL. She was admitted for autologous hematopoietic stem cells transplantation in the specialized bone marrow transplant center, medical city complex, Iraq. She previously took etoposide without significant allergy. According to the National Health Service protocols, the LEAM has been started as a conditioning regimen within 6 days before transplantation (from day – 6 to day – 1). LEAM protocol consists of lomustine, etoposide, cytarabine, and melphalan, as shown in Table 1.

All laboratory tests were normal on admission [Table 2]. The patient's body surface area has been calculated using Mosteller formula[15] and found to be 1.8 m^2. Other anthropometric measurements are also reported in Table 3.

About 360 mg of etoposide was administered in 1000 ml of normal saline (0.9% NaCl). The doses were divided into two bags infused over 2 h; the first bag is 200 mg of etoposide in 500 mL of 0.9% NaCl administered over 1 h and the second bag is 160 mg of etoposide in 500 mL of 0.9% NaCl over 1 h, on day – 5 to day – 2 (4 days).

Table 1: LEAM protocol

Drug	Dose (mg/m^2)	Days
Lomustine	200	On day - 6
Etoposide	200	On day - 5 to day - 2 (4 days)
Cytarabine	200	On day - 5 to day - 2 (4 days)
Melphalan	140	On day - 1
Transplantation stem cells		On day Zero (day 0)

M^2=Body surface area, LEAM=Lomustine, etoposide, cytarabine, and melphalan

Table 2: Laboratory test

Patient Lab report	Value
HB	13.1
WBC	8.3
PLT	169
Urea	32.9
Scr	0.5
Na	137
K	3.8
AST	26.5
ALT	35.7
ALK	87.5
TSB	0.4

HB=Hemoglobin, WBC=White blood cells, PLT=Platelet, Scr=Serum creatinine, Na=Sodium, K=Potassium, TSB=Total serum bilirubin, ALK=Alkaline phosphatase, AST=Aspartate aminotransferase, ALT=Alanine aminotransferase

Table 3: Patient details

Gender	Female
Age	26 years
Height	160 cm
Weight	73 kg
BSA	1.8 m^2

BSA=Body surface area

On day – 5 (the 1st day of the etoposide dose), the patient noticed a slight rash on some areas of the abdomen.

The mild rash persisted slightly until the – 3 day of LEAM protocol, after which a bacterial infection occurred, therefore, the patient was started on Tazocin (piperacillin + tazobactam) to treat the bacterial infection.

On the last day of the etoposide dose (day – 2), severe sensitivity to etoposide occurred, represented by severe skin rash, high temperature, a drop in blood pressure of 81/42, a drop in saturated oxygen level to 87%, and an increase in heart rate to 93 bpm, forcing the doctor to stop the dose of etoposide and give hydrocortisone 100 mg, diphenhydramine 10 mg, and oxygen. To ascertain the possibility that the drug is the cause of hypersensitivity, the Naranjo score was calculated and it was equal to 6, which indicates that the drug caused the hypersensitivity reaction.[16]

One hour later, the patient's condition improved, as shown in Table 4.

After talking to the patient, it was found that she previously suffered from a mild allergy to penicillin.

Discussion

Hypersensitivity reactions to chemotherapy and other treatments are not rare.[17] The mechanism of these allergies is not fully understood. Etoposide is a chemotherapeutic agent, which has been used in the treatment of different types of cancers including blood cancer. Allergy to etoposide has been reported in many studies. Some studies stated that the allergy to etoposide was immune-mediated and others indicated that histamine secretion is the main component in these allergic reactions.[18]

Allergic reactions to penicillin are common.[19] In our case, our patient was allergic to etoposide, and her allergic reaction was aggravated by the administration of Tazocin.

The risk factors for hypersensitive to etoposide are unknown.[17] To the best of our knowledge, this study is the first study that reported the presence of a cross-allergic reaction between penicillin and etoposide which needs further investigation.

Table 4: Vital signs during and after administration of etoposide

Vital signs@	Blood pressure	Pulse rate	Temperature	Saturation oxygen (%)
With etoposide	81/42	93	38.5	87
After stopping etoposide	94/59	78	35.7	97

The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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