

Delayed urticaria with oxaliplatin

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Oxaliplatin (trans-L, 1,2 diamino-cyclohexane oxaliplatinum) is a third generation platinum salt that is mainly used to treat metastatic colorectal cancer in combination with fluorouracil and folinic acid.

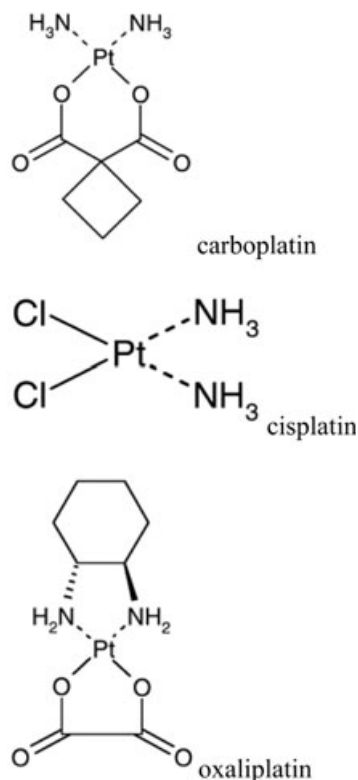
Hypersensitivity reactions to platinum salts are known to be potential adverse events during chemotherapy (1–4) and seem to be less frequent with oxaliplatin than with cisplatin or carboplatin (5, 6). The frequency of immediate reactions to oxaliplatin has been estimated between 1% and 12% (6–8). Skin tests should be performed to confirm the role of oxaliplatin and to exclude cross-reactivity with other platinum salts before substituting one analogue by another (6).

Many cases of urticaria with oxaliplatin have been described in the literature (8–14) and severe symptoms (even life-threatening), such as hypotension, angioedema and anaphylactic shock may occur. Several mechanisms have been put forward to explain immediate reactions (i.e.

IgE-mediated (15), idiosyncratic (16, 12) and type III delayed urticarial vasculitis (17)).

We report the case of a 66-year-old woman with a metastatic colon cancer treated with oxaliplatin and 5-fluorouracil, who developed an urticarial rash 8 days after the third course of chemotherapy.

Structures of carboplatin, cisplatin and oxaliplatin :



Case Report

A 66-year-old woman with a history of colon cancer treated by chemotherapy presented with a widespread rash that had appeared 2 days earlier, 8 days after her third IV-infusion of oxaliplatin and 5-fluorouracil for colon adenocarcinoma with hepatic metastases found 6 months earlier. The two previous cycles of chemotherapy were devoid of any skin side effects.

The rash was a generalized urticaria with a transient angioedema of the lower lip and accompanied by severe pruritus. Lesions were recurring urticarial papules with a typical

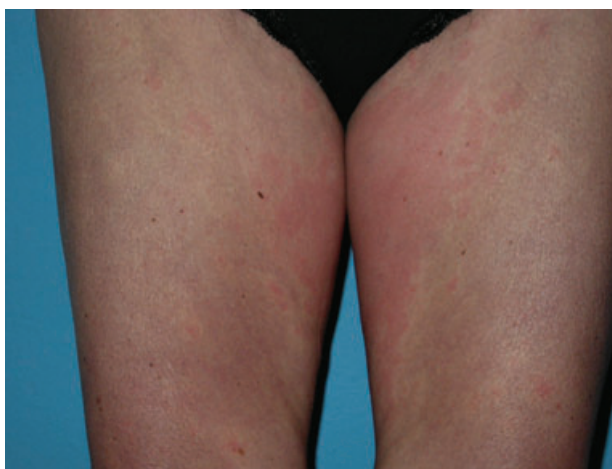


Fig. 1. Urticarial rash with typical peripheral halo of vasoconstriction.

peripheral halo of vasoconstriction regressing within 24 hr with no residual purpura (Fig. 1). There was no bronchospasm or hypotension.

Before the onset of the rash, the patient had been taking lorazepam and paracetamol daily, but she had not taken acetylsalicylic acid or any other anti-inflammatory drug. There was no personal or family history of drug allergy. Additional pertinent past medical history included breast cancer treated 8 years previously by surgery, chemotherapy (epidryamycine, cyclophosphamide, methotrexate, fluorouracil), radiotherapy and tamoxifen during a 5-year period.

The histopathological examination of a skin biopsy showed an inflammatory infiltrate of lymphocytes, histiocytes and neutrophilic cells around dermal vessels and scattered in the dermis. There were no signs of vasculitis, the latter was confirmed by immunohistopathological examination. There were no deposits of IgG, IgM, IgA or complement (C3, C1q) around the vessels.

The chemotherapy courses were stopped. The rash disappeared completely after 2 days of treatment with antihistamines (initially fexofenadine and then desloratadine and levocetirizine). The antihistamines were stopped after 2 weeks, without any further recurrence of the urticarial reactions.

Six weeks after the first consultation, prick tests were performed on the forearm with injectable forms of oxaliplatin and 5-fluorouracil using a glucose 5% solution and codeine phosphate 9% as negative and positive controls, respectively. Positive

reactions were defined as a 3-mm or larger wheal at 20 min. In addition, the sites were examined at 1D and 2D. The results were negative after 20 min and also at the later readings.

Solutions of oxaliplatin in glucose 5% and a solution of 5-fluorouracil in NaCl 0.9%, both at dilutions 10^{-3} and 10^{-2} were prepared for intradermal tests. The dilutions were prepared 1 hr before injection under laminar flow.

Intradermal tests were performed in the forearm by injecting 0.05 ml of each solution. Glucose 5% and NaCl 0.9% were used as negative controls. For intradermal tests to be considered positive, a 2-fold increase in the diameter of the initial wheal after 30 min was required.

Oxaliplatin intradermal test at the dilution 10^{-3} was positive after 30 min. This result was confirmed with the dilution 10^{-2} after 30 min (Fig. 2). Later readings (D1, D2 and D3) were negative in all cases.

The same tests carried out in a subject who had not had any skin reaction with oxaliplatin were negative.

To check for possible cross-reactions with the other platins, tests were performed with two other molecules: i.e. carboplatin and cisplatin. A positive reaction to carboplatin was observed: a prick test was negative but intradermal tests with carboplatin at dilutions of 10^{-3} and 10^{-2} were positive after 30 min (Fig. 3). Tests with cisplatin were completely negative.

Discussion

While urticaria to oxaliplatin is a well known adverse event during oxaliplatin chemotherapy, delayed reactions



Fig. 2. Positive oxaliplatin intradermal skin test at dilution 1/100 after 30 minutes.



Fig. 3. Positive oxaliplatin and carboplatin intradermal skin tests at dilution 1/100 after 30 minutes.

appearing 8 days later do not seem to be commonly observed.

Calvo et al. (18) reported the case of a 66-year-old man with rectal carcinoma who presented with a non-itchy urticarial eruption on the neck 24 hr after the first course of oxaliplatin chemotherapy. This eruption relapsed during the second course, but improved with oral antihistamines and corticosteroids. Prick tests were negative but intradermal tests were followed by a delayed erythematous infiltrated rash that appeared a day later. The patient also developed a relapse of the rash on his neck.

Other authors (17) described the case of a 56-year-old woman diagnosed with rectal carcinoma and pulmonary metastasis, who developed a generalized urticarial and pruritic rash 8 days after the fourth course of intravenous oxaliplatin. There was no angioedema. The eruption also improved after

4 days of oral antihistamines and corticosteroids. Despite negative prick tests and intradermal tests after 20 and 30 min, respectively, a delayed erythema and infiltration appeared a day later.

A third case of a delayed hypersensitivity reaction consisting of severe respiratory symptoms during about 24 hr, without skin eruption, following the 1st and the 2nd infusions of oxaliplatin, has also been described (19).

The immunological mechanism of delayed urticaria to oxaliplatin is unknown; the theory of an immunological reaction as a result of a circulating immune complex has been proposed (17).

Cross-reactions between oxaliplatin and carboplatin seem to be rare but more frequent than between oxaliplatin and cisplatin (6). In our patient, the cross-reaction with carboplatin was

confirmed by positive intradermal tests.

This is the first case of a generalized urticarial rash occurring 8 days after an oxaliplatin infusion, and confirmed by positive immediate intradermal tests.

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