

Cutaneous adverse drug reactions during chemotherapy: consider non-antineoplastic drugs

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Cutaneous adverse drug reactions (CADR) during chemotherapy are not rare, but difficult to manage. Case 1, a 49-year-old man was treated with 5-fluorouracil, irinotecan, and oxaliplatin for a pancreatic tumour. He developed a generalized urticaria during his seventh course of chemotherapy. 2 months later, skin tests determined a granisetron allergy with an ondansetron cross-reaction. Substituting the anti-emetic allowed continuation of the chemotherapy. Case 2, a 44-year-old woman, having recurring breast cancer that was treated with doxorubicin, and docetaxel developed a maculo-papular rash (MPR) the day after the first chemotherapy treatment. 2 weeks later, skin tests determined a corticosteroid class A allergy. Using a class C corticosteroid, no other reaction occurred. Case 3, a 44-year-old woman, having breast cancer treated with 5-fluorouracil, cyclophosphamide, and epirubicin developed an MPR after the second chemotherapy treatment. 12 days later, skin tests showed a granisetron allergy. Using alizapride, chemotherapy was con-

tinued with no further reaction. CADR necessitate a thorough investigation, modified according to the patient's chemotherapy treatment chronology and precautions while testing the molecules. Tests are rarely carried out, however, these tests allow for continuation of effective chemotherapy once the responsible agent has been determined. The 3 cases reported underline the role of complementary treatment and the necessity to test those molecules.

Key words: antineoplastic drug; cutaneous adverse drug reaction; hypersensitivity; setrons; skin tests; systemic steroids.

Cutaneous adverse drug reactions (CADR) with antineoplastic chemotherapy are not uncommon, but are difficult to manage because of the fact that associated treatments, not the antineoplastic drug, may be responsible. The 3 reported cases emphasize the necessity of a thorough investigation because associated treatments may be responsible for CADR.

Case Report

Case 1

A 49-year-old man suffering from a pancreatic tumour with liver metastasis received 5-fluorouracil, irinotecan, and oxaliplatin. He also received granisetron and methylprednisolone as anti-emetic drugs. During his 7th chemotherapy treatment, he developed a generalized urticaria 20 min after the oxaliplatin injection. The urticaria disappeared in less than 1 hr after a second methylprednisolone injection. Skin tests [patch tests, prick tests, and intradermal tests (IDT) (0.04 ml on the arm)] were performed 2 months later with antineoplastic drugs and setrons. The IDT with granisetron in an undiluted aliquot showed a positive result on 20 min reading (3 negative controls), and the IDT for ondansetron was positive on 20 min reading with 0.2 mg/ml (6 negative controls), confirming a granisetron allergy with an ondansetron cross-reaction (Table 1). Using another anti-emetic drug (alizapride), the chemotherapy could be continued and was well tolerated.

Case 2

A 44-year-old woman with breast cancer was initially treated with a combined therapy of surgery and chemotherapy (cyclophosphamide,

methotrexate, and 5-fluorouracil). A few years later, she had a relapse of the breast cancer and received a second course of chemotherapy with doxorubicin, docetaxel and prednisolone, granisetron, and metoclopramide. The day after the first chemotherapy treatment, she developed a maculopapular rash (MPR). It began with a pruritic palmar erythema, spreading to become a generalized rash. Prednisolone was discontinued 36 hr later, and the MPR disappeared within 15 days with an antihistamines. Patch tests, prick tests, and IDT were performed 2 weeks later with antineoplastic drugs, corticosteroids, and setrons (Table 1). Patch tests with tixocortol-21-pivalate, 0.1% pet. and the

powder for the injection of methylprednisolone diluted at 30% in pet., in water, and in alcohol were positive on D2 and D4 readings, determining a corticosteroid class A allergy (1). No previous history of topical corticosteroid sensitivity or any risk factor such as atopic dermatitis or leg ulcers was noticed. This drug was substituted with a class C corticosteroid (betamethasone), and chemotherapy was continued without cutaneous side-effects.

Case 3

A 44-year-old woman, diagnosed with breast cancer, was initially treated with 5-fluorouracil, cyclophospha-

mid, and epirubicin with methylprednisolone (which was switched to prednisolone a few days after) and granisetron (which was switched to domperidone and ondansetron a few days after the chemotherapy course). She developed an MPR the day after the second chemotherapy course, initially localized on her legs, spreading to a generalized rash. The rash rapidly disappeared in 3–4 days with an antihistamines. Patch tests, prick tests, and IDT with antineoplastic chemotherapy, corticosteroids and setrons were carried out 12 days later, and indicated a granisetron allergy as the IDT was positive on immediate reading with 0.2 mg/ml drug dilution without cross-reaction

Table 1. Skin tests performed in the 3 cases reported

		Patch test at 48 and 96 hr	Prick tests at 20'	Prick tests at 24 hr	IDT at 30'	IDT at 24 hr
Case 1	Carboplatine® (oxaliplatin) 10% aq., pure	—				
	Cisplatyl® (cisplatin) 10% aq., pure	—				
	Eloxatine® (eloxatine) 10% aq., pure	—				
	Solumédrol® (methylprednisolone) pure	—				
	Kytril® (granisetron) 30% aq., alc, pure	—				
	Zophren® (ondansetron) 30% aq., alc, pure	—				
	Carboplatine® 0.1 and 1 mg/ml	—				
	Cisplatyl® 0.05 and 0.5 mg/ml	—				
	Eloxatine® 0.05 and 0.5 mg/ml	—				
	Zophren® 0.0002–2 mg/ml		—	—	+ at 0.2 mg/ml	—
Case 2	Kytril® 0.0001–1 mg/ml		—	—	+ at 1 mg/ml	—
	Doxorubicine® (doxorubicin) 0.1% aq.	—				
	Taxotère® (docetaxel) 0.1% aq.	—				
	Zophren® (ondansetron) 30% pet.	—				
	Primpéran® (alizapride) 30% aq., pet., alc	—				
	Médrol® (methylprednisolone) 30% aq., pet., alc	+				
	Budesonide 0.1% pet.	—				
	Tixocortol-21-pivalate 0.1% pet.	+				
	Betametasone 0.12% pet.	—				
	Aclomethasone 1% pet.	—				
Case 3	17 Butyrate of hydrocortisone 0.1% pet.	—				
	Doxorubicine® 0.1% aq.		—	—	ND	
	Taxotère® 0.1% aq.		—	—	ND	
	Solumédrol® (methylprednisolone) pure	—				
	Farmorubicine® (epirubicin) 10% aq., pure	—				
	Endoxan® (cyclophosphamide) 10% aq., pure	—				
	5 FU® (5-fluorouracil) 10% aq., pure	—				
	Zophren® (ondansetron) 30% aq., pure	—				
	Kytril® (granisetron) 30% aq., pure	—				
	Budesonide 0.1% pet.	—				
	Tixocortol-21-pivalate 0.1% pet.	—				
	Betametasone 0.12% pet.	—				
	Aclomethasone 1% pet.	—				
	17Butyrate of hydrocortisone 0.1% pet.	—				
	5 FU® 3.125 mg/ml		—	—	ND	
	Endoxan® 1 mg/ml		—	—	ND	
	Farmorubicine® 1 mg/ml		—	—	ND	
	Zophren® 0.2–2 mg/ml		—	—	+ at 0.2 mg/ml	—
	Kytril® 0.1–1 mg/ml		—	—	+ at 1 mg/ml	—
	Solumédrol® 0.625–62.5 mg/ml		—	—	—	—

alc, dilution in alcohol; aq., dilution in water; IDT, intradermal test; ND, not done; —, negative; pet., dilution in petrolatum; +, positive.

to ondansetron (Table 1). Using alizapride, chemotherapy could be continued with no stronger reaction than a corticosteroid flush.

Discussion

Skins eruptions during antineoplastic chemotherapy can be due to an infection (viral or bacterial, often due to immunosuppression), a paraneoplastic syndrome, pharmacological drug skin toxicity, or a drug allergy (all types of hypersensitivity can be seen) (2–4). CADR are not rare and should always be investigated, especially because of the difficulties in finding a replacement molecule that has the same efficacy as the suspected drug (5). This requires thorough investigation, taking into account associated treatments. Moreover, it is often necessary to adapt the investigations to the patient's chemotherapy treatment chronology, performing skin tests between courses of chemotherapy. Usually, skin tests are performed 6 weeks after the disappearance of the CADR, in order to distance it from the initial reaction, with no further immune modifications that could disturb skin reactivity or induce a severe reactivation of the CADR. As our reported cases show, and in order to continue the chemotherapy treatment, we performed skin tests a short time after the disappearance of the CADR, with no severe reaction. While testing with antineoplastic drugs, certain precautions are mandatory: nurses must use gloves, hats, and masks while preparing the tests, as these drugs can cause cutaneous necrosis. There is no standardized procedure on how to perform skin testing with antineoplastic drugs. In our department, we use patch tests with drugs diluted at 1% or 10% in water, prick tests with the same dilutions, but no IDT. Some authors perform IDT with an undiluted aliquot of platinum salts (6, 7). With skin tests, delayed positive results mainly occur in type IV hypersensitivity and immediate positive results in type I hypersensitivity. But less frequently, as observed in our third case and as previously reported (8, 9), immediate reactions on IDT can occur in patients who had developed a delayed MPR.

As shown in the reported cases, chemotherapy treatments are not always responsible for CADR. It is important to test all associated treat-

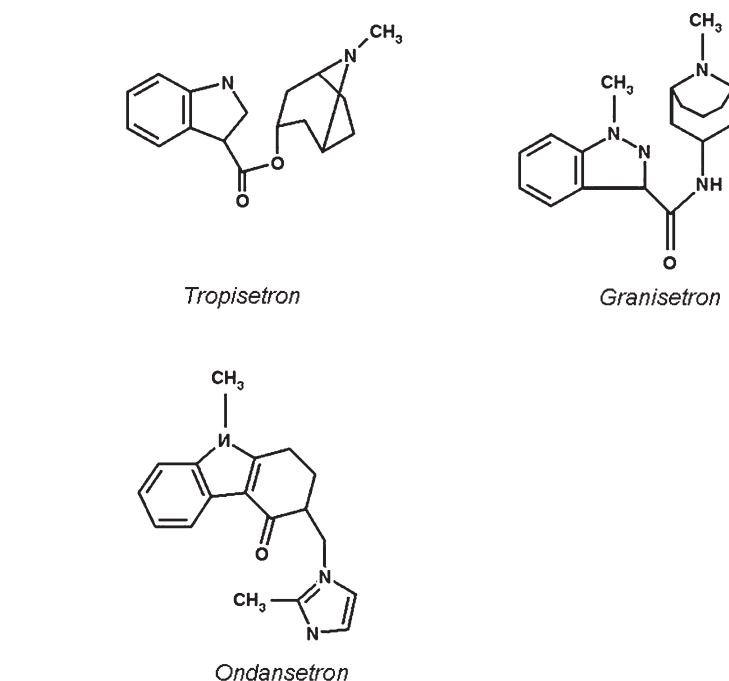


Fig. 1. Setron chemical structures.

ments such as anti-emetic drugs, analgesics, or anxiolytics. A few cases of setron allergy, mainly due to type I hypersensitivity, have been published (10–13). Cross-reactions between tropisetron and ondansetron have been described as a class effect. But these 2 molecules share an indole heterocycle (14, 15). As ondansetron and granisetron have a divergent heterocycle (Fig. 1), it was supposed that there could be no cross-reaction between those 2 molecules (16). We emphasize that cross-reactions can occur, as observed in our first case report. Therefore, skin tests should be performed whether deemed necessary or not, so that molecules in this therapeutic class can be adequately substituted.

Allergy to systemically administered corticosteroids is rare when compared with how frequently they are prescribed, but does exist (17, 18). To our knowledge, corticosteroid allergy during chemotherapy treatment has not previously been described. Skin tests with corticosteroids are difficult to interpret because of the inflammatory power of these molecules. Therefore, testing with high dilutions of these drugs and performing delayed readings on D7 are important. Both patch tests and IDT can be useful in investigating CADR because of corticosteroids (18). Corticosteroid substitutions must be performed in accordance to the chem-

ical and allergological classification of these drugs (1).

Conclusion

The 3 cases reported underline the fact that treatments associated with chemotherapy can induce adverse drug reactions and the necessity of testing these molecules. Otherwise, a chemotherapy treatment might be unjustifiably discontinued while continuing the associated treatment, leading to a new CADR flare-up. Careful investigation with a sequential series of skin tests can be of great help in determining the responsible drug and finding a replacement molecule which permits the continuation of effective chemotherapy, as documented in our cases.

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