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Allergic-type reactions to oxaliplatin: Retrospective analysis of 42 patients

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Abstract

Oxaliplatin is a platinum salt that is particularly effective in treating gastrointestinal tumours. Its increased use has resulted in emergence of allergic reactions, including anaphylactic shock.

Allergic reactions to oxaliplatin documented over the last 5 years have been analysed using predefined criteria. The 42 analysed patients had cancer and received a FOLFOX regimen in first line or beyond. Two types of allergy were observed: a type I immediate allergic reaction in 39 patients in whom the most frequent signs were respiratory (50%) and cutaneous (40%); anaphylactic shock that occurred in three patients; type II allergy (immunological thrombopenia) was observed in three patients. All the toxicities were reversible on symptomatic treatment. No predictive factor was evidenced.

Anaphylactic shock, is rare but serious, and must be considered in the event of any severe blood pressure decrease. For the non-life-threatening reactions, prolonging infusion duration, "Stop and Go" regimen seem to be effective means of preventing recurrence.

Keywords: Allergy; Anaphylaxis; Oxaliplatin; Thrombopenia

1. Introduction

Oxaliplatin has become one of the major cytotoxics for the treatment of colorectal cancer and other tumours, particularly gastrointestinal. Increased use of oxaliplatin has enabled the detection of a rare allergy adverse event that was not exceptionally reported in the first clinical trials (0.55%) [1].

Allergic reactions are mediated by a reaction between antigen and antibodies or sensitised lymphocytes. Four types of allergy are to be distinguished. Type I allergy is an immediate hypersensitivity reaction. It results from the degranulation of mast cells and basophils following IgE binding to those cells. Various cytokines with strong inflammatory potential are also released and contribute to the emergence of the clinical signs: bronchoconstriction and vasodilatation are the most critical symptoms of anaphylactic shock. Type II allergy conventionally results in hemolytic anemia or thrombopenia through activation of complement and killer cells. Type III allergy, whose clinical signs include fever, chronic urticaria, joint pain, proteinuria, vasculitis and pneumonia, involves the deposit of immune complexes in certain tissues. The last type of allergy, type IV, mediated by T cells, induce an inflammatory reaction whose results may be contact dermatitis or inflammatory granuloma [2].

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Allergy to platinum salts (cisplatin, carboplatin) is classically a type I, *i.e.*, immediate reaction. Allergy to platinum salts – reported to be due to the platinum atom – is the second most frequent after allergy to asparaginase [3].

Oxaliplatin is diaminocyclohexane (DACH) platinum that differs from the other platinum drugs in terms of its activity spectrum (particularly active in colorectal cancer) and toxicity (mainly neurological). The authors, through their experiences, tried to determine predictive factors of occurrence of allergic reactions and to define the optimum management of that adverse reaction.

2. Patients and methods

Patients had to have been treated with oxaliplatin in combination, in first or subsequent lines, for a malignant tumour, and to have presented with an allergic reaction considered treatment-related from 3 September 1997 to 24 November 2003. The patient files had to be sufficiently documented to enable analysis of the allergic reaction. The following data were collected: gender; age; known allergy to other platinum salts; type of cancer; treatment regimen; treatment line; type of allergic reaction and date of occurrence; oxaliplatin dose administered and cumulative dose of oxaliplatin (mg/m^2) received; and the number of courses administered when the episode occurred. The treatment of the allergic reaction, time course of the episode with recovery date, continuation or withdrawal of oxaliplatin, and any recurrence of the allergic episode after oxaliplatin rechallenge were analysed.

3. Results

Forty-two cases of allergic reactions to oxaliplatin occurring between September 1997 and November 2003 were analysed and patients characteristics are shown in Table 1. They were mainly treated with the FOLFOX 7 (38%) or FOLFOX 4 regimens (24%) (Tables 2 and 3). No patient presented with a known history of allergy to a platinum salt. As expected, the most frequently observed symptoms were respiratory (50%) and cutaneous (40%), presenting as a type I immediate allergy (Table 4). The symptoms rapidly resolved, in a few minutes, on simple symptomatic treatment. The outcome for the patients was variable (Fig. 1).

Three cases of real anaphylactic shock occurred. Two of them were observed on second and third course of reintroduction of oxaliplatin (allergic reaction was absent during first line treatment with oxaliplatin). The third case occurred on the sixth treatment. The outcome was positive following appropriate treatment and oxaliplatin was definitively withdrawn.

Three other patients presented with severe immunoallergic thrombopenia (platelets $< 2000/mm^3$) related to type II allergy, after 2, 15 and 24 courses of oxaliplatin, respectively. The oxaliplatin doses at which thrombopenia occurred were 130 mg/m^2 (cumulative dose: 200

Table 1
Patient characteristics ($n = 42$)

Characteristics	*N* (%)
Gender: male/female	12/30
Median age (range)	63 (range: 20–86)
Cancer diagnosis	
Colorectal	32 (76.2)
Pancreas	4 (9.5)
Biliary duct system	3 (7.1)
Uterine sarcoma	1 (2.4)
Ovary carcinoma	1 (2.4)
Breast carcinoma	1 (2.4)
Extent of disease	
Metastatic	40 (95.2)
Locally advanced[a]	2 (4.8)

[a] Pancreas.

Table 2
Treatment characteristics

Treatment	*N* (%)
Folfox 7[a]	16 (38.1)
Folfox 4[a]	10 (23.8)
Gemox	10 (23.8)
Folfox 6[a]	8 (19.0)

One patient was treated with FOLFOX 7 then FOLFOX 6.
[a] One patient was treated with FOLFOX 4 then FOLFOX 6.

Table 3
FOLFOX 4, 6 and 7 administered every 14 days

	H0	H2	H24	H48
FOLFOX 4	FA 400	5FU bolus 400	FA 400	5FU bolus 400
	Oxaliplatin 85	5 FU CI 600	5FU CI 600	
FOLFOX 6	FA 400	5FU bolus 400		
	Oxaliplatin 100		5FU CI 2400	
FOLFOX 7	FA 400			
	Oxaliplatin 130		5FU CI 2400	

Dose mg/m^2.
One cycle every 14 days.

Table 4
Allergic reactions

Characteristics	*N* (%)[a]
Serious reactions	
Anaphylactic shock (type I)	3 (7.1)
Immunologic thrombopenia (type II)	3 (7.1)
Other reactions (type I)	
Respiratory symptoms	20 (47.6)
Cutaneous reactions	17 (40.5)
Generalised reactions	14 (33.3)
Digestive symptoms	8 (19.0)

Anaphylactic shock is defined as severe hypotension, associated with malaise and others symptoms as bronchospasm, erythema, prurit, Quincke edema, digestive symptoms. Respiratory symptoms include bronchospasm, laryngospasm, dyspnea. Cutaneous reactions include erythema, edema, Quincke edema, prurit, urticaria. Generalised reactions include fever, chills, malaise, sweats. Digestive symptoms include nausea, vomiting, abdominal pain.

[a] One patient could have more than one symptom.

mg/m^2) for the first patient, and 100 mg/m^2 (cumulative doses: 1380 and 2400 mg/m^2) for the other two. After steroid treatment and platelet transfusions, the platelet level was maintained above 50 000/mm^3 between 10 days and 3 weeks after the event. Oxaliplatin was definitively withdrawn from treatment for all three patients.

The type I allergic reactions excluding anaphylactic shock occurred after administration of a median number of oxaliplatin courses of 7 (range: 1–14). The cumulative median oxaliplatin dose received was 650 mg/m^2 (range: 100–2400). The symptoms observed were mainly respiratory (48%): bronchospasm, laryngospasm and dyspnea. Skin rashes occurred in 41% of cases and consisted of erythema, edema, angioedema, pruritus and urticaria. A systemic reaction occurred in one out of three of the patients (fever, rigors, malaise and sweating) and 19% of the patients had a type I allergic reaction with gastrointestinal signs (nausea, vomiting, abdominal pain). No death occurred (Table 5).

The episode of allergy was reversible on appropriate symptomatic treatment for all patients within minutes, hours or, for the immunological fevers, a few days.

The follow up of patients is detailed in Fig. 1.

4. Discussion

Two different types of allergy were observed and are to be distinguished: immediate type I allergy occurring in the majority of patients (39 patients) and type II allergy in the form of immunoallergic thrombopenia (3 patients). Allergy to oxaliplatin has already been reported with a frequency ranging from 2% (5/250 patients) [4] to 14% (17/124 patients), depending on the publication [5–8]. In the largest clinical trial with oxaliplatin-MOSAIC-involving 2246 patients, 10.6% of them experienced allergic reaction, but only 2.9% grade 3–4 [26].

Since most of the publications are case reports, it is difficult to grade the severity of the symptoms. Respiratory signs of grade II on the Ring-Messmer severity scale [9] (Table 6) and erythema of grade I (30%) on the same scale were observed. These results are comparable to those reported by Brandi *et al.* [8] and Thomas *et al.* [1]. In all cases reported, the toxicity was rapidly reversible following infusion discontinuation and appropriate treatment [1,5,10]. Although most of the case reports describe anaphylactic shock [11–15], the present series only included three cases out of 42 allergic reactions and no episode was reported in two published series consisting of 25 and 17 allergic episodes, respectively [1,8].

A special feature of the type I allergic reaction occurring in oxaliplatin treatment is the late onset and unpredictable nature of the event: in the series reported herein, the median number of oxaliplatin courses was 7. This is compliant with what has already been reported: four [1] to seven courses [5,7]. The allergic reaction may even occur in the 17th course [8]. The chemotherapeutic status (single-agent or FOLFOX-type combination chemotherapy), single or cumulative dose, and chemotherapeutic line (first line *vs.* second or subsequent lines) do not seem to have any influence on the occurrence of allergic episodes [1]. All the episodes occurred in the minutes following infusion initiation. This is characteristic of type I allergy. Those situations can be immediately treated with antihistamines or steroids. For such patients, oxaliplatin may be reintroduced, with an increase in the infusion duration from 4 to 6 h, without any particular pre-medication (Table 7). Published data suggest that prevention of the risk with steroids and antihistamines is debatable [1,4,8,11,15].

In this group of type I allergies, anaphylactic shock is to be distinguished. The latter is a veritable medical emergency and the prognosis is not to be underestimated. As of the slightest onset of disorders, blood pressure must systematically be determined. Any marked decrease in blood pressure during oxaliplatin infusion should immediately point to anaphylactic shock and is to be treated as such by appropriate emergency measures (steroids, antihistamines, plasma expanders, oxygen, possibly epinephrine). Transfer to intensive care may be required if the signs do not regress rapidly. In such cases, oxaliplatin must not be re-administered.

The type II, immunoallergic thrombopenia, was observed in three patients. Definitive withdrawal of oxaliplatin is strongly suggested after a sudden and severe thrombopenia (Table 7), while Dold and Mitchell also reported cases of thrombopenia (17th course) in 2003.

We also observed late occurrence of immunoallergic thrombocytopenia in two patients (15th and 24th

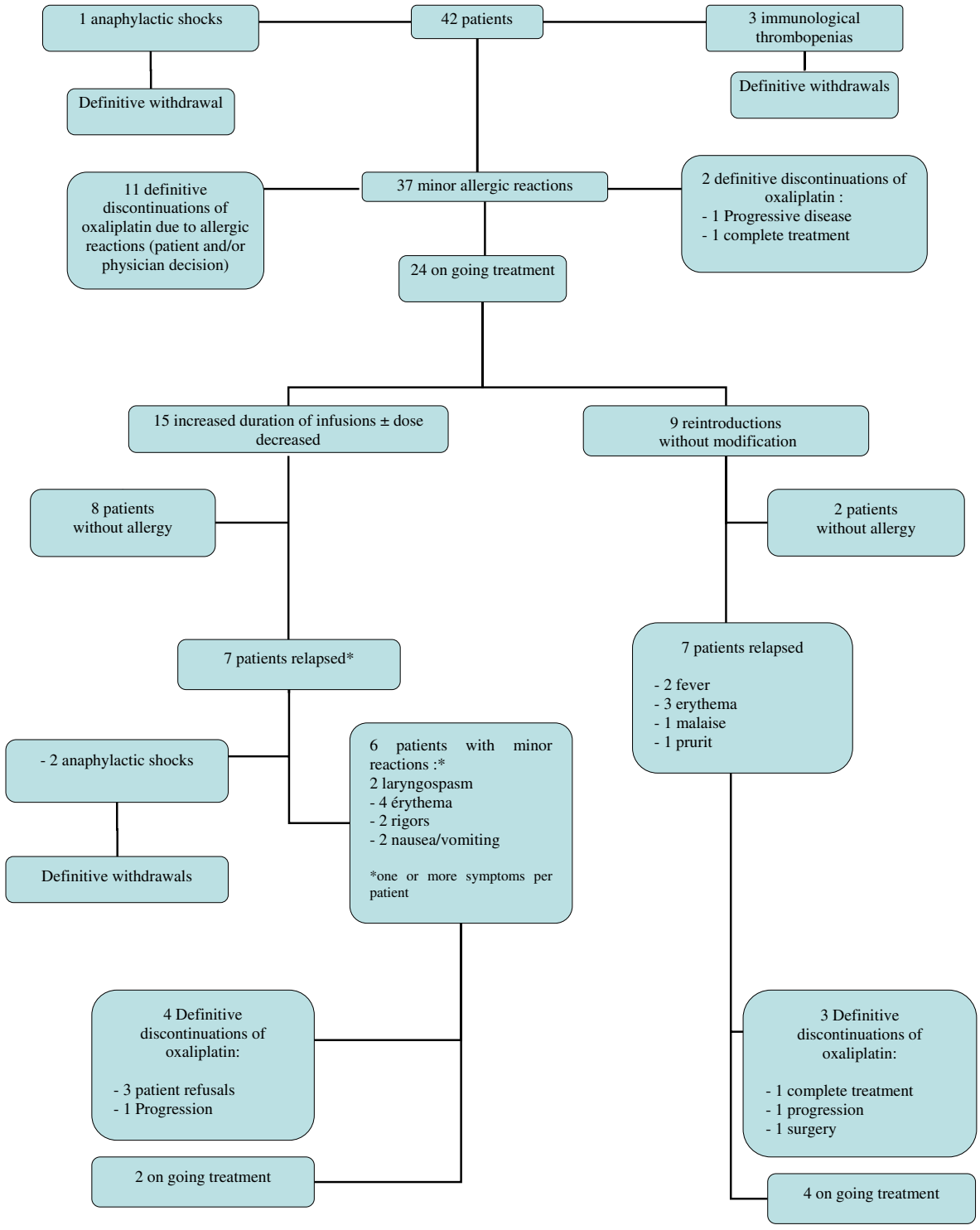

Fig. 1. Follow up of patients presenting allergic reactions to oxaliplatin.

courses). Immunohemolytic anemia has been reported twice in settings of oxaliplatin treatment and is related to an antibody reaction due to the platinum atom [16,17]. A type III allergy mediated by circulating immune complexes has been described only once. The reaction consisted in urticaria emerging on day 8 of the fourth course of oxaliplatin in a 56-year old woman treated with FOLFOX for metastatic colorectal cancer. The symptoms regressed completely in 4 days on treatment with antihistamines and steroids [18].

We did not use systematic pre-medication but prefer to increase the duration of infusion (Table 7). Several authors have reported this to be an effective means of preventing the recurrence of the allergic event [1,5,8].

Table 5
Desensitisation protocol per administration

Dose no.	Total dose (mg)	Concentration (mg/ml)	Duration of infusion (min)
1	1	0.02	1
2	2.5	0.05	3
3	5	0.1	5
4	10	0.2	10
5	25	0.5	25
6	50	1	50
7	100	2	100

From Lin and colleagues [24].

Table 6
Severity scale of anaphylactic reaction

Grade	Symptoms
I	Skin symptoms and/or mild fever reaction
II	Measurable, but not life-threatening, cardiovascular reaction (tachycardia hypotension), gastrointestinal disturbances(nausea), respiratory disturbance
III	Shock, life-threatening spasm of smooth muscles (bronchi, uterus etc)
IV	Cardiac and/or respiratory arrest

From Ring and Messmer [9].

Table 7
Recommendations for allergic reactions occurring with oxaliplatin

Symptoms	Category of allergy	Recommendations
Laryngospasm, bronchospasm, dyspnea, erythema, prurit, edema, edema, urticaria fever, chills, malaise, sweats nausea, vomiting, abdominal pain	Type I	Duration of infusion from 2 to 4 or 6 h± preventive treatment with dexchlorpheniramine
Anaphylactic shock	Type I	Definitive discontinuation of oxaliplatin
Severe immune thrombopenia	Type II	Definitive discontinuation of oxaliplatin

It should however be noted that, even without preventive measures, recurrence is not systematic. The following episode may be less severe. In contrast, a number of factors exacerbate the symptoms, such as β-blocker intake, heart failure and/or coronary artery disease, a history of asthma or mitral valve prolapse [19].

Oxaliplatin treatment allows good results in gastrointestinal tumours in particular, and withdrawal of oxaliplatin is thus prejudicial for patients for whom the therapeutic resources are limited.

Several teams have attempted to predict the risk of recurrence by confirming oxaliplatin allergy by skin tests. Prick tests are usually negative. In contrast, intradermal oxaliplatin injections yield contradictory results [7,18,21,22]. Successful desensitisation was also described by different authors [6,23–25].

New strategies restricting treatment duration to six courses of FOLFOX, followed by pauses in treatment ('Stop and Go') will perhaps limit the occurrence of allergic reactions. In the present authors' series, the allergic episode emerged after a median number of courses greater than 7. Although, in the event of a response or no-change on treatment, the patients can resume a new series of six courses if disease progression occurs [20].

Due to the development of oxaliplatin use, the unpredictable increase in the frequency of allergic reactions necessitates setting up effective and simple measures enabling allergic patients to continue oxaliplatin treatment. Treatment with that drug is essential, particularly for gastrointestinal tumours. Anaphylactic shock, although rare, remains a life-threatening emergency. It is easy to diagnose (blood pressure measure) and treat as such. Reintroduction of oxaliplatin is formally contra-indicated for that type of patient as well as for immune thrombopenia. For non-life-threatening reactions, increasing the infusion duration up to 6 h is recommended. Patient desensitisation seems of interest because of its consistent efficacy, but this has only been demonstrated in a small number of subjects. Moreover, desensitisation is cumbersome to implement. The optimum desensitisation regimen in terms of efficacy and dispensation needs to be defined. Treatment strategy is a key point: "Stop and Go" regimen, with alternating "on treatment" and "off treatment" periods and currently evaluated in on going "Optimox" studies may, perhaps, be a solution.

Conflict of interest statement

All authors disclose any financial and personal relationships with other people or organisations that could inappropriately influence their work.

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