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Hypersensitivity reactions to platinum-based compounds in the context of pressurized intraperitoneal aerosol chemotherapy (PIPAC): description and management

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1 To the Editor,
2 Pressurized intraperitoneal aerosol chemotherapy (PIPAC) consists of intraperitoneal
3 administration of aerosol platinum salt (PS) chemotherapy under general anesthesia, oxaliplatin
4 (PIPAC-Ox) mostly in the case of colorectal cancer, and cisplatin with doxorubicin (PIPAC-CD)
5 in the case of ovarian and other digestive cancers(**Repository text**). It can also be alternated with
6 intravenous (IV) chemotherapy [1]. Systemic toxicity is low, with almost no kidney or liver
7 toxicity[2].It is increasingly used [3].Only one study described four patients with PS IgE-mediated
8 allergy to PIPAC[4].

9 We present here our own experience with drug allergy work-up and management options for
10 patients suffering an IgE-mediated HR to PS, in the context of PIPAC.The allergy work-up
11 included ST performed according to the European Network on Drug Allergy
12 recommendations[5].All patients gave their informed consent for their anonymous data to be used
13 for research purposes. We retrospectively searched the database of the Department of Surgical
14 Oncology at the Cancer Institute of Montpellier for (i) patients who had suffered an allergic
15 reaction during PIPAC procedures between July 2016 and December 2019, or (ii) who needed
16 PIPAC PS in the context of a suspicion of IV PS allergy.A total of 230 PIPAC procedures were
17 performed on 79 patients. Thirty-nine patients had PIPAC-Ox, 40 patients had PIPAC-CD. One in
18 each group was eventually switched to PIPAC with mitomycin C. Within this cohort, five patients
19 fulfilled the following inclusion criteria: (i) HR during PIPAC to PS or (ii) HR to PS by IV route
20 and reexposure to PIPAC (**Figure 1**).

21
22 **Table 1** presents the patients characteristics and drug allergy work-up. All these patients had
23 previously been exposed to PS(IV and/or PIPAC) prior to the onset of the reaction.

24
25 Two patients presented grade I and III respectively HR, both of them with oxaliplatin[6]. These
26 patients had benefited from PIPAC procedures regularly, every 6 weeks. The allergic reaction
27 occurred during the 5th PIPAC for patient 1 and the 12th for patient 2. Patient 2 developed aHR at
28 the end of the 2nd electrostatic PIPAC (**Repository Text**).They reacted at 70 and 55 min,
29 respectively, after the beginning of PIPAC (and 40 minutes after the end of the procedure for
30 both). Patient 2 first developed cutaneoussymptoms, followed 15 minutes later by anaphylactic
31 shock. For both, the allergy work-uprevealedpositive ST to oxaliplatin and negative ST for

cisplatin and carboplatin. Both were subsequently authorized, but other alternatives were preferred.

The other three patients experienced a reaction to oxaliplatin and/or carboplatin during IV chemotherapy (grade I to grade III). Patient 3 had positive ST with oxaliplatin and carboplatin. Despite inconclusive intradermal test (IDT), patient 4 was considered allergic and oxaliplatin was contraindicated. These two patients could afterwards uneventfully receive PIPAC-CD. Patient 5 benefited from PIPAC-CD without allergic recurrence; no allergy referral was made and no ST were performed.

Four patients with IgE-mediated allergy to PIPAC-CD and Ox chemotherapy have been previously described by Siebert et al [4]. All presented with anaphylaxis. Three of them had had previous administrations of IV PS. Allergy was confirmed by prick tests. Definitive contraindication to all PS-based PIPAC was advocated and no reexposure was attempted.

In our case series, two patients experienced reactions during PIPAC-Ox (incidence: 5.1%; 95% confidence interval, 1.4% to 16.9%), three reacted with IV PS and went on to successfully receive PIPAC with a ST negative PS. Cross-reactivity between PS is known, especially between oxaliplatin and carboplatin [7], due to very similar chemical structure. Although the number of patients in our series is small, it appears that negative ST could predict good tolerance in PIPAC procedure as it is known for the IV route. As desensitization is not an option for PIPAC considering its unique mode of administration, investigation for alternative PS is of utmost importance. Tolerance to the alternative ST-negative PS would be confirmed after a negative drug provocation test (DPT) performed in specific either allergy [8] or oncology units to ensure patient safety.

As PIPAC is performed under general anesthesia, it is important to test any additional drug administered before and during the procedure. In the case of our patients, appropriate ST and specific IgE were performed to exclude the involvement of any other agents. The high negative predictive value of ST to anesthetic drugs and the rarity of simultaneous multiple drug allergy in immediate reactions are all the more reason to support the diagnosis of IgE-mediated allergy to PS.

64 Knowledge on the natural history of allergy to IV PS shows that IgE-mediated reactions occur
65 after the patient has undergone multiple courses of treatment, on average at the 7th-8th
66 administration. For some authors[8-9], there is a specific phenotype who reacts typically after the
67 therapy is resumed with the same PS agent, following a hiatus of more than 6-12 months since the
68 previously tolerated cycles. In the case of PIPAC, the treatment is usually administered every 6
69 weeks, with no interruption. Since only some of the PIPAC reactive patients had previously well
70 tolerated IV PS, direct sensitization by the PIPAC route is possible.

71
72 One of the patients experienced anaphylaxis during electrostatic PIPAC, a variant of PIPAC first
73 described in 2016. The reaction occurred at the end of the procedure. It should be kept in mind that
74 the systemic uptake is limited after PIPAC and that timing of the reaction can possibly differ with
75 this type of administration, as compared to the IV one. However, the addition of electrostatic
76 precipitation to PIPAC-Ox was recently shown to be associated with important systemic uptake
77 [10].

78
79 Patient 5 had a reaction to oxaliplatin and benefited from PIPAC with cisplatin without allergy
80 investigations and without allergic recurrence. No allergy referral was made in that case, so the
81 diagnosis of allergy to oxaliplatin was not thoroughly confirmed. The fact that the patient could
82 receive cisplatin despite a probable allergy to oxaliplatin is in agreement with Pasteur et al. who
83 showed that cisplatin can be administered safely in patients with a history of carboplatin or
84 oxaliplatin allergy as long as it has never been used before[7]. Therefore, patients should not be
85 contraindicated to PIPAC based solely on a history of HR to another platinum compound.

86
87 In summary, allergists should be aware of this mode of administration and its peculiarities,
88 compared to the IV route, namely a greater delay between administration and HR, probably
89 related to the delay associated to intraperitoneal absorption and/or the lower systemic uptake.
90 Allergy work up performed by expert allergists, with ST (prick and IDT), identifies safe
91 alternatives for PIPAC exposure among the different PS agents, just like it does for allergy to IV
92 PS. Multidisciplinary work, especially between the surgical/oncology team and the allergist, is
93 important to find and further administer these alternatives in a safe environment.

94

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Table 1. Summary of patients' characteristics.

Patient Sex/Age	Allergy history	Medical history	Primary cancer	Chemotherapy used before the reaction			Chemotherapy involved in index DHR	Symptoms	Grade of reaction †	Drug allergy work-up	Chemotherapy used after allergy assessment
				1st line	2nd line	3rd line					
Patient 1 M/83 y	-Allergic rhinitis -Alleged DHR to Codeine	-Coronary artery disease -Pulmonary embolism	Appendiceal	PIPAC -Oxaliplatin	-	-	Oxaliplatin (5th PIPAC)	Skin eruption of the abdomen and limbs	Grade I	Positive: Oxaliplatin (SPT at 1 mg/mL and IDT at 0.001 mg/mL) ‡ Negative: Cisplatin and Carboplatin	PIPAC -Mitomycin C
Patient 2 M/52 y	-Allergic rhinitis	-Obesity	Gastric	IV -Cisplatin -Epirubicin -Capecitabin	IV -LV-5FU -Oxaliplatin -Docetaxel	ePIPAC -Oxaliplatin	Oxaliplatin (12th PIPAC, 2nd ePIPAC)	Tachycardia, hypotension and erythema	Grade III	Positive: Oxaliplatin (SPT at 1 mg/mL) Negative: Cisplatin and Carboplatin	IV -5-FU -Irinotecan
Patient 3 F/65 y	-	-Arterial hypertension	Ovarian	IV -Carboplatin -Paclitaxel	-	-	Carboplatin IV	Trunk and hand urticaria	Grade I	Positive: Carboplatin (IDT at 1 mg/mL) and Oxaliplatin (IDT at 0.1 mg/mL) Negative: Cisplatin	PIPAC -Cisplatin -Doxorubicin IV -Paclitaxel
Patient 4 M/63 y	-Contact urticaria to plaster	-Chronic obstructive pulmonary disease	Colorectal	IV -LV-5FU -Oxaliplatin -Irinotecan	IV -LV-5FU -Oxaliplatin -Bevacizumab	-	Oxaliplatin IV	Erythema of the face, vomiting, pruritus, desaturation	Grade III	Inconclusive: Oxaliplatin (IDT at 0.1 mg/mL) ~ Negative: Cisplatin and Carboplatin	PIPAC -Cisplatin -Doxorubicin
Patient 5 F/44 y	-	-Deep vein thrombosis	Gastric	PIPAC -Cisplatin -Doxorubicin	IV -LV-5FU -Oxaliplatin -Docetaxel	IV -LV-5FU -Oxaliplatin	Oxaliplatin IV	Pruritus, erythema and edema of the hand, foot and lips, abdominal pain, muscular contraction	Grade II	ND	PIPAC -Cisplatin -Doxorubicin or -Mitomycin C

Abbreviations: **ePIPAC:** Electrostatic Pressurized intraperitoneal aerosol chemotherapy, **DHR:** drug hypersensitivity reaction; **F:** female, **5-FU:** 5-fluorouracil, **IDT:** Intradermal test, **IV:** intravenous, **LV-5FU:** leucovorin and 5-fluorouracil, **ND:** Not done, **PIPAC:** pressurized intraperitoneal aerosol chemotherapy **SPT:** Skin Prick Test, **y:** years

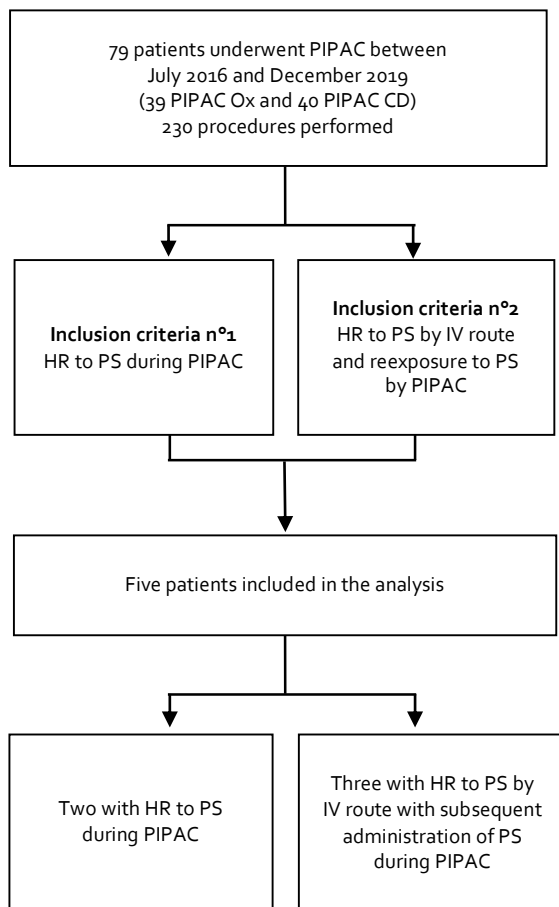
† According to Ring and Messmer [8]

‡ The IDT was performed at 0.001 mg/mL to confirm the positivity of the SPT. The positivity of SPT was surprising, because of the grade I reaction and the delay of occurrence (see text).

~ Considered positive based on clinical history and response in skin test with erythema 31/25 mm and increase of the initial bleb by 1 mm

Patient 2 was the only patient with tryptase measurement available during the reaction showing a significant increase (11.1 ug/mL) compared to baseline (1.2X4.5+2 = 7.4), Patient 1: baseline tryptase 8.3 ug/mL

Figure 1: Flow-chart of the study.



HR, hypersensitivity reaction

IV, intravenous

PIPAC, pressurized intraperitoneal aerosol chemotherapy;

PIPAC Ox, PIPAC with oxaliplatin

PIPAC CD, PIPAC with cisplatin and doxorubicin

PS, platinum salt

Repository text PIPAC

Pressurized intraperitoneal aerosol chemotherapy (PIPAC)

The procedure is increasingly used for patients with unresectable peritoneal carcinomatosis or when patients are not candidates for cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy [1]. The first systematic review accounted for 801 procedures in 2017 [1] while a recent international survey performed in 2019 declared 5972 procedures worldwide [2].

The procedure is performed under general anesthesia. A capnoperitoneum of 12 mmHg is insufflated and ascites is drained, if any. Exploratory laparoscopy is performed, the peritoneal cancer index (PCI) accounting for the extension of the peritoneal disease is performed and parietal biopsies are taken. A pressurized aerosol containing oxaliplatin 92 mg/m² body surface in 150 mL dextrose is applied in the case of colorectal cancer and some digestive cancers, or cisplatin 10.5 mg/m² body surface in 150 mL NaCl 0.9% associated with doxorubicin 2.1 mg/m² body surface in 50 mL NaCl 0.09% for other origins. The administration is performed at 0.5-0.7ml/s at a maximal upstream pressure of 290 PSI (20 bar). The system is kept in a steady-state for 30 minutes, and the aerosol is exhausted in a closed wasting system. The average PIPAC procedure lasts 90 minutes and can be repeated every 6 to 8 weeks. Doses used are about 1/10 of the usual IV dosage for PIPAC-CD and similar to the usual IV for PIPAC-Ox. PIPAC can be an option when patients have unresectable peritoneal metastasis or when patients are not candidates for cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) [1]. HIPEC is administered post cytoreductive surgery and consists of heated chemotherapy delivered in the abdominal cavity and removed after a maximum of two hours. The protocol for PIPAC differs from HIPEC, in the sense that the drug

is delivered as a pressurized aerosol in the peritoneal cavity and that PIPAC can be repeated various times. It can also be alternated with systemic chemotherapy [3].

Compared to HIPEC, PIPAC is associated with a better drug distribution in the intraperitoneal cavity and with increased depth of penetration.

Electrostatic Pressurized intraperitoneal aerosol chemotherapy (ePIPAC)

Electrostatic PIPAC is a procedure during which a current of $\leq 10 \mu\text{A}$ and 7,500-9,500 V is added. Electrostatic loading is used as an adjunct to induce precipitation of the aerosolized drug and improve tissue uptake [4]. It was observed that the aerosol vanished within seconds after activation of the generator. The activation is performed either at the beginning or at the end of the injection and the post-activation administration time is not standardized as the reports from different teams range from 1 to 30 minutes.

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