



HAL
open science

Low Cross-Reactivity Between Cisplatin and Other Platinum Salts

Justine Pasteur, Laure Favier, Corinne Pernot, Mathieu Guerriaud, Charlotte Bernigaud, Côme Lepage, Jean-Louis Jouve, Nicolas Isambert, Evelyne Collet

► **To cite this version:**

Justine Pasteur, Laure Favier, Corinne Pernot, Mathieu Guerriaud, Charlotte Bernigaud, et al.. Low Cross-Reactivity Between Cisplatin and Other Platinum Salts. *Journal of Allergy and Clinical Immunology: In Practice*, 2019, 7, pp.1894 - 1900. 10.1016/j.jaip.2019.01.057 . hal-03487989

HAL Id: hal-03487989

<https://hal.science/hal-03487989>

Submitted on 20 Dec 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 Manuscript

2

3 **TITLE PAGE**

4

5 **Title**

6

7 Low cross-reactivity between cisplatin and other platinum salts.

8

9 **Authors**

10 Justine Pasteur, M.D.¹ Laure Favier, M.D.² Corinne Pernot, M.D.³ Mathieu Guerriaud, Ph.D.⁴

11 Charlotte Bernigaud, M.D.¹ Côme Lepage, M.D. Ph.D.⁵ Jean-Louis Jouve, M.D.⁵ Nicolas

12 Isambert, M.D.² Evelyne Collet, M.D.¹

13

14 **Affiliations**

15 ¹ Dermatology Department, Dijon University Hospital, Dijon, France

16 ² Oncology Department, Centre Georges-François Leclerc, Dijon, France

17 ³ Pharmacy Department, Dijon University Hospital, Dijon, France

18 ⁴ University of Burgundy, Dijon, France

19 ⁵ Gastroenterology Department, Dijon University Hospital, Dijon, France

20

21 **Corresponding author:**

22 Justine Pasteur, M.D.

23 Service de dermatologie, Centre Hospitalier Universitaire, Hôpital François Mitterrand,

24 14 rue Paul Gaffarel,

25 BP77908, 21079 Dijon Cedex, France

26 E-mail: justine.pasteur@chu-dijon.fr

27 Phone: +33 3 80 29 33 36

28 Fax: +33 3 80 29 30 28

29

30 **Conflict of interest:** none

31

32 **Abstract**

33 **Background:** Hypersensitivity reactions to platinum salts (PS) (cisplatin (CI), carboplatin
34 (CA) and oxaliplatin (OX)) can be severe and their incidence is increasing due to their
35 widespread use in cancer treatment.

36 **Objective:** To determine the rate of cross-reactivity between platinum salts and whether
37 CI can be administered without prior allergy testing in patients with a history of CA or
38 OX hypersensitivity.

39 **Methods:** From September 2002 to April 2016, patients with suspected immediate PS
40 hypersensitivity were tested and cross-reactivity between the three PS was evaluated. We
41 then studied patients who were given cisplatin without desensitization after immediate
42 hypersensitivity to other PS.

43 **Results:** A total of 155 patients were included. Skin tests were positive in 97 patients
44 (OX: 51, CA: 43 and CI: 3). Cross-reactivity to CA in OX-allergic patients was 45%
45 (23/51) (95%CI: 36% to 66%) and cross-reactivity to OX in CA-allergic patients was 37%
46 (16/43) (95%CI: 23% to 53%). In contrast, cross-reactivity to CI was 0% (0/51) (95%CI:
47 0% to 7%) in OX-allergic patients and 7% (3/43) (95%CI: 2% to 17%) in CA-allergic
48 patients. All these 3 patients had previously been exposed to CI in previous courses of
49 chemotherapy. CI was initiated in 24 patients with proven hypersensitivity to CA or OX
50 and had no hypersensitivity reactions.

51 **Conclusion:** Initiating CI in patients with proven immediate hypersensitivity to CA or OX
52 appeared to be safe in our study.

53

54 **Highlights Box:** □

55 1. What is already known about this topic? The management of immediate
56 hypersensitivity to platinum salts consists in carrying out skin testing and setting up a
57 desensitization protocol. Moreover, cross-reactivity between the three platinum salts is a
58 matter of debate.

59

60 2. What does this article add to our knowledge? This study demonstrates that cross-
61 reactivity between carboplatin and oxaliplatin □ is very frequent whereas cross-reactivity
62 between cisplatin and the other platinum □ salts is rare. The use of cisplatin after
63 hypersensitivity to carboplatin or oxaliplatin appears □ safe. □

64

65 3. How does this study impact current management guidelines? If desensitization can not
66 be proposed and in the accordance with oncologist, cisplatin can be administered safely in
67 patients with a history of carboplatin or oxaliplatin hypersensitivity provided it has never
68 been used before.

69

70 Keywords: Allergy, Immediate hypersensitivity, Platinum salt, Cross-reaction, Skin
71 testing, Chemotherapy, Intradermal test, Anaphylaxis.

72

73

74 **Abbreviations**

75

76 **CA** Carboplatin

77 **CI** Cisplatin

78 **IDTs** Intradermal Tests

79 **LDH** Lactate dehydrogenase

80 **OX** Oxaliplatin

81 **PS** Platinum salt

82 **INTRODUCTION**

83 Platinum salts (PS) (cisplatin (CI), carboplatin (CA) and oxaliplatin (OX)) are commonly
84 used for the treatment of various cancers such as colorectal, pancreatic and ovarian
85 cancer¹⁻⁷. Immediate hypersensitivity reactions to PS are frequent and estimated at 15 to
86 20% in different studies, and can be severe⁸⁻¹⁴. Hypersensitivity reactions to PS are
87 generally observed after a mean of eight infusions^{13,15}, although recent studies have shown
88 that they can appear earlier^{1,2,16}. Different studies have identified various potential risk
89 factors linked to hypersensitivity: the interval between the end and the resumption of
90 treatment if more than two years¹⁷, total dose received^{9,18}, age¹⁹, history of drug allergy¹⁷,
91 HLA DR3²⁰, and high serum lactate dehydrogenase (LDH) level at the beginning of
92 chemotherapy²¹.

93 For diagnosis, skin testing especially intradermal tests (IDTs) are commonly used²²⁻²⁴.
94 Many authors^{1,22,25} demonstrated that IDTs are reliable and have a good negative
95 predictive value.

96 Currently, the incidence of cross-reactivity between the three PS is unclear, although some
97 studies in a small number of cases have shown that switching to CI in patients with CA or
98 OX hypersensitivity was safe in a majority of patients²⁶⁻²⁸.

99 When an allergic reaction occurs during an infusion of PS, treatment is immediately
100 stopped and all three PS are contraindicated until consultation with a specialist and skin
101 allergy testing. Desensitization is considered safe and supported by many publications.

102 If desensitization is not an option, could cisplatin be safely used in patients reactive to
103 oxaliplatin or carboplatin in accordance with oncologist?

104 The aim of this study was to determine the rate of cross-reactivity in patients receiving PS
105 in a teaching hospital in France and whether CI can be administered without prior allergy
106 testing in patients with a history of CA or OX hypersensitivity.

107
108
109
110

111 **METHODS**

112 We conducted a retrospective, descriptive, single-center study from September 2002 to
113 April 2016 at the Dermatology Department of Dijon University Hospital, France. Patients
114 coming for a dermato-allergology consultation for immediate hypersensitivity reactions to
115 PS were included. An immediate reaction to PS was defined as a reaction that occurs
116 during the infusion or within 1 hour after the infusion of one of the three PS (CA, OX or
117 CI). Skin tests were performed after a minimum of 4-6 weeks after resolution of the
118 hypersensitivity reaction. Indeed, false negative skin testing is possible if it is too early
119 after the hypersensitivity reaction probably due to a period of “anergy” after a systemic
120 reaction.^{25,29}

121 Intradermal tests (IDTs) were performed by using a sterile solution of each PS (active
122 product and excipients): Cisplatine Accord® (cisplatin, injectable form, 100mg/100ml;
123 Accord Healthcare France), Carboplatine Hospira® (carboplatin, injectable form,
124 450mg/45ml; Hospira, France) and Oxaliplatine Hospira® (oxaliplatin, injectable form,
125 100mg/20ml; Hospira, France) diluted in 0.9% saline successively according to the
126 following sequence (1/1000, 1/100 and 1/10). Dilutions were prepared following a
127 standardized procedure at the Dijon University Hospital Pharmacy Department under
128 laminar flow 2 hours before injection. IDTs were performed on the patients’ upper back
129 by injecting 0.02 mL of sterile dilutions, which produced a 4 mm to 6 mm wheal. IDTs
130 were considered positive if the diameter of the wheal measured 3 mm more than the
131 diameter of the initial one after 20 minutes.

132 All concomitant treatments and/or premedications (corticosteroids, antiemetic agents,
133 other chemotherapy agents) were also tested if suspected, according to the European
134 Society of Contact Dermatitis guidelines for drug skin testing³⁰.

135 After the dermatology consultation and IDTs, the oncologist was consulted to choose the
136 most appropriate PS that was negative during the test to be used for the patient. The drug
137 was then initiated at the therapeutic dose and regimen, without desensitization. Any
138 hypersensitivity reactions were assessed.

139 In addition, clinical data were collected: age of the patient, sex, cancer type, number of
140 courses administered until a reaction occurred and symptoms of the hypersensitivity
141 reaction. Symptoms were graded according to Brown’s classification³¹.

142

143 **RESULTS**

144 **Patients**

145 During the 14-year study period, 184 patients had investigations for hypersensitivity
146 reactions to PS. Among these patients, 29 were not analysed because they had a delayed
147 rather than immediate reaction. Finally, 155 remaining patients with immediate
148 hypersensitivity were included (see figure 1). Patients' clinical data are summarized in
149 Table I.

150 **Treatments and hypersensitivity reactions**

151 The suspected PS was CA in 64 cases, OX in 87 cases and CI in 4 cases. The median
152 number of courses administered until the reaction occurred was nine (range: 1-37). Eleven
153 patients had already received another treatment with a different PS in the past (CA: 5, OX:
154 2 and CI: 4). Clinical signs of immediate hypersensitivity to the PS were grade 1 (mild) in
155 30% (47/155), grade 2 (moderate) in 62% (96/155) and grade 3 (severe) in 8% (12/155)
156 according to Brown's classification³¹. The most common symptoms were cutaneous
157 manifestations in 107 patients (107/155: 69.0%). These cutaneous signs were urticaria,
158 pruritus, erythema and angioedema. Other manifestations are detailed in Table II. There
159 were six cases of anaphylactic shock, which occurred during the drug infusion.

160 **Skin tests**

161 Skin tests were positive to the suspected PS in 97 of the 155 patients (62.6%) (CI: 3 cases,
162 CA: 43 cases, OX: 51 cases). Tests were thus negative for 58 patients (58/155: 37.4%)
163 and two hypersensitivities to concomitant treatment were seen: one positive test for
164 epirubicin (Farmorubicine®, Pfizer) anthracycline chemotherapy and another for
165 raniditine (Azantac®, GlaxoSmithKline) an antagonist of histamine receptor type 2
166 (Figure 1). No incidents occurred during the test procedures.

167 Among patients with positive skin tests, 41 patients were positive to more than one PS.
168 Thirty-eight patients had positive IDTs to CA and OX, two patients had positive IDTs to
169 CA and CI and only one had positive IDTs to all three PS. Cross-reactivity to CA in OX-
170 allergic patients was 45% (23/51) (95%CI: 36% to 66%) and cross-reactivity to OX in
171 CA-allergic patients was 37% (16/43) (95%CI: 23% to 53%). In contrast, cross-reactivity
172 to CI was 0% (0/51) (95%CI: 0% to 7%) in OX-allergic patients and 7% (3/43) (95%CI:
173 2% to 17%) in CA-allergic patients but those 3 patients had been previously exposed. In

174 the 38 cases of cross-reactivity between CA and OX, only two patients had received the
175 two PS successively. The results about the different positive skin tests are resumed in
176 Table III.

177 **Drug re-exposure**

178 After skin testing, the oncologists decided to reinfuse PS in 58 patients (30 patients with
179 positive tests and 28 patients with negative tests). The choice of PS was made by the
180 oncologists and the PS was reinfused without any particular precautions and at the
181 recommended dose.

182 Among the 28 with negative tests: 16 patients were re-exposed to the same PS (CA: 6 and
183 OX: 10), and 12 patients to another PS (CA: 1, OX: 2 and CI: 9). No hypersensitivity
184 reactions were notified.

185 Among the 97 patients to which skin tests were positive, 30 patients were re-exposed with
186 another PS: 24 with CI, two with CA and four with OX; and one patient was desensitized
187 with OX. There were no reactions during the administration (Table IV).

188 Al together, 33 patients were given cisplatin. These patients were given between one and
189 24 cycles of cisplatin (mean 9 cycles). No patients experienced hypersensitivity reactions.
190 The treatment was stopped for three reasons: renal failure, deterioration of the patient's
191 general health status, or lack of efficacy.

192

193 **DISCUSSION**

194 Hypersensitivity to PS was first described by Hunter et al. in 1945 among employees
195 working in a refinery³². Since then, the incidence of hypersensitivity has risen due to the
196 widespread use of PS in many cancers treatments. Skin testing has proven to be helpful in
197 the diagnosis of IgE-mediated hypersensitivity to a platinum salt.^{22,25,29}

198 We present here, a study with a large number of patients tested after immediate
199 hypersensitivity to PS. Our study included 155 patients with the same baseline
200 epidemiological profile as other published studies on hypersensitivity to PS^{10,26,33,34}.

201 To date, the incidence of cross-reactivity between the three most widely used PS is not
202 well-established. Some rare previous studies have demonstrated cross-reactivity between
203 PS based on skin tests^{35,36}. In a majority of studies about hypersensitivity to PS, skin tests
204 have been performed just with the suspected PS, and cross-reactivity has been not
205 investigated¹. Brault et al. have found only one case of cross-reactivity between CA and
206 OX in 14 patients with positive IDTs to PS³⁷. All IDTs to CI were negative. In our study,
207 we showed for the first time that cross-reactivity between CA and OX was very frequent:
208 cross-reactivity to CA was 45% in OX-allergic patients and cross-reactivity to OX was
209 37% in CA-allergic patients with only two patients who had received both PS in the past.
210 This finding therefore probably reflects a true cross-reactivity. In contrast, cross-reactivity
211 between CI and OX or CA was rare: 0% in OX-allergic patients and 7% in CA-allergic
212 patients. In our study, there were no cases of cross-reactivity between CI and other PS
213 when CI had never been used in previous courses of chemotherapy. To our knowledge,
214 this observation has never been described in the literature.

215 The different chemical structures of the PS could explain this phenomenon (Figure 2). The
216 three molecules are different and have various pharmacological properties: CI is a
217 diaminodichloroplatin, CA is cyclobutane-dicarboxyloplatin, and OX is a diaminohexane-
218 platin derivative. The first hypothesis suggested by Caiado et al.³⁸ was that the central
219 platinum atom was an epitope. They supported ~~her~~ their theory by showing the presence
220 of platinum specific IgE. Our testing results, however, did not confirm this hypothesis.
221 Indeed, the active metabolites do not seem to be involved in cross-reactivity because CI
222 and CA are transformed into the same diaquaplatin after hydrolysis and these two PS were
223 less involved in cross-reactivity in our study. We therefore propose a new hypothesis,

224 namely that the nitrogen-platinum-oxygen-carbon-oxygen-carbon chain (N-Pt-O-CO-C),
225 which is present only in CA and OX and not in CI, could be the common epitope
226 explaining cross-reactivity.

227 Moreover, our study showed that there were no hypersensitivity reactions when CI was
228 initiated in patients with hypersensitivity to CA and OX, when CI had never been used
229 before. In the same way, several studies have shown that re-exposure with CI after OX or
230 CA hypersensitivity is safe^{3,8,28,36,39-46}. To date, only Zweizig et al.⁴⁷, Shelbak et al.⁴⁸ and
231 Dizon et al.²⁶ have reported hypersensitivity reactions following a switch to CI. There
232 were four cases of patients who received CI after a hypersensitivity reaction to CA and
233 subsequently developed a severe reaction to CI. Analysis of these four cases showed that
234 all of these patients had received CI several years previously for the first treatment of the
235 cancers. Callahan et al.²⁷ and Bergamini et al.⁴⁵ also reported eleven cases of
236 hypersensitivity to CI at re-exposure after a hypersensitivity reaction to CA. In ten cases,
237 the reaction developed after a median of 3 courses of CI. In our opinion, these cases
238 cannot be regarded as a failure of the re-exposure, but as a new hypersensitivity to CI. In
239 our study, no patient re-exposed to CI experienced hypersensitivity reaction. In two cases
240 of the Callahan et al.²⁷ and the Ottaiano et al.⁴⁹ studies, patients experienced a reaction to
241 CI during the first infusion of the re-exposure. Unfortunately, we do not have enough
242 information to analyze these hypersensitivity reactions as we do not know if the patient
243 had previously been treated with CI.

244 In 2015, Kolomeyevskaya et al.³⁹ proposed the reintroduction of OX in patients with an
245 allergy to CA, without a skin test. Our results go against this strategy because our tests
246 showed a high frequency of cross-reactivity between CA and OX.

247 The results of all these different studies are summarized in Table V.

248 When patients experience a hypersensitivity reaction during PS infusion, treatment
249 should be stopped immediately. The collaboration between allergist and oncologist is
250 essential. After patient's risk stratification, as proposed by Giavina-Bianchi et al.⁵⁰ based
251 on the severity of the initial reaction, the patient's comorbidities and the drug given to the
252 patients, several possibilities can be proposed to the oncologist. If the oncologist wants to
253 continue the same PS, skin testing should be done as soon as possible. If these tests are
254 positive, desensitization is the best option. Indeed several studies have reported that
255 desensitization is a safe and effective method.^{29,25,37,50} However, this approach needs to be
256 used repeatedly before each infusion. If the oncologist wants to change for any reason, the
257 best approach is skin testing with the three PS: OX, CA and CI. If the oncologist chooses

258 CI, the risk of immediate hypersensitivity reaction seems very low as shown in this study.
259 In our experience, this option can be useful in gynecologic cancer but less so in digestive
260 cancer as the three PS are not equivalent in terms of efficacy and tolerance. If skin testing
261 is negative, a drug provocation test or regular infusion can be proposed based on the risk
262 stratification⁵⁰. As the administration of chemotherapy is far from risk-free, the benefit-
263 risk ratio must always be evaluated. Moreover, patients should be advised about the risk
264 and closely monitored by experienced medical staff.

265 **Figure legends**

266

267 **Figure 1.** Flowchart of the study. 155 patients had immediate hypersensitivity to PS and were
268 included in the retrospective study.

269

270 **Figure 2.** Chemical structure of cisplatin (a), carboplatin (b) and oxaliplatin (c) molecules are
271 presented in this figure. The N-Pt-O-CO-C chain present in both carboplatin and oxaliplatin is
272 highlighted in the blue diagram.

273

274

275 **Acknowledgements**

276

277 We thank the nurses for consultations and the secretaries of the Dermatology Department,

278 Dijon University Hospital, Dijon, France, the staff of the archives of Centre Georges-François

279 Leclerc, Dijon, France and Mr Philip Bastable, Research Unit at Dijon University Hospital.

280

281 **References**

282

- 283 1. Wong JT, Ling M, Patil S, Banerji A, Long A. Oxaliplatin hypersensitivity: evaluation,
284 implications of skin testing, and desensitization. *J Allergy Clin Immunol Pract*. 2014
285 Feb;2(1):40–5.
- 286 2. Park H, Lee J, Kim S, Kim S, Park K, Lee C, et al. A New Practical Desensitization
287 Protocol for Oxaliplatin-Induced Immediate Hypersensitivity Reactions: A Necessary
288 and Useful Approach. *J Investig Allergol Clin Immunol*. 2016 Jun 20;26(3):168–76.
- 289 3. Shukunami K, Kurokawa T, Kubo M, Kaneshima M, Kamitani N, Kotsuji F.
290 Hypersensitivity reaction to carboplatin during treatment for ovarian cancer: successful
291 resolution by replacement with cisplatin. *Tumori*. 1999 Aug;85(4):297–8.
- 292 4. Shibata Y, Ariyama H, Baba E, Takii Y, Esaki T, Mitsugi K, et al. Oxaliplatin-induced
293 allergic reaction in patients with colorectal cancer in Japan. *Int J Clin Oncol*. 2009
294 Oct;14(5):397–401.
- 295 5. Syrigos KN, Karachalios D, Karapanagiotou EM, Nutting CM, Manolopoulos L,
296 Harrington KJ. Head and neck cancer in the elderly: An overview on the treatment
297 modalities. *Cancer Treat Rev*. 2009 May;35(3):237–45.
- 298 6. Raymond E, Faivre S, Chaney S, Woynarowski J, Cvitkovic E. Cellular and molecular
299 pharmacology of oxaliplatin. *Mol Cancer Ther*. 2002 Jan;1(3):227–35.
- 300 7. Kelland L. The resurgence of platinum-based cancer chemotherapy. *Nat Rev Cancer*.
301 2007 Aug;7(8):573–84.
- 302 8. Polyzos A, Tsavaris N, Kosmas C, Arnaouti T, Kalahanis N, Tsigris C, et al.
303 Hypersensitivity reactions to carboplatin administration are common but not always
304 severe: a 10-year experience. *Oncology*. 2001;61(2):129–33.
- 305 9. Navo M, Kunthur A, Badell ML, Coffey LW, Markman M, Brown J, et al. Evaluation of
306 the incidence of carboplatin hypersensitivity reactions in cancer patients. *Gynecol*
307 *Oncol*. 2006 Nov;103(2):608–13.
- 308 10. Maindrault-Goebel F, André T, Tournigand C, Louvet C, Perez-Staub N, Zeghib N, et
309 al. Allergic-type reactions to oxaliplatin: retrospective analysis of 42 patients. *Eur J*
310 *Cancer Oxf Engl 1990*. 2005 Oct;41(15):2262–7.
- 311 11. Lee M-Y, Yang M-H, Liu J-H, Yen C-C, Lin P-C, Teng H-W, et al. Severe anaphylactic
312 reactions in patients receiving oxaliplatin therapy: a rare but potentially fatal

- 313 complication. *Support Care Cancer Off J Multinatl Assoc Support Care Cancer*. 2007
314 Jan;15(1):89–93.
- 315 12. Wang J-H. Oxaliplatin-induced severe anaphylactic reactions in metastatic colorectal
316 cancer: Case series analysis. *World J Gastroenterol*. 2012;18(38):5427.
- 317 13. Sliesoraitis S, Chikhale PJ. Carboplatin hypersensitivity. *Int J Gynecol Cancer Off J Int*
318 *Gynecol Cancer Soc*. 2005 Feb;15(1):13–8.
- 319 14. Makrilia N, Syrigou E, Kaklamanos I, Manolopoulos L, Saif MW. Hypersensitivity
320 Reactions Associated with Platinum Antineoplastic Agents: A Systematic Review. *Met-*
321 *Based Drugs*. 2010;2010:1–11.
- 322 15. Markman M, Kennedy A, Webster K, Elson P, Peterson G, Kulp B, et al. Clinical
323 features of hypersensitivity reactions to carboplatin. *J Clin Oncol Off J Am Soc Clin*
324 *Oncol*. 1999 Apr;17(4):1141.
- 325 16. Parel M, Ranchon F, Nosbaum A, You B, Vantard N, Schwiertz V, et al.
326 Hypersensitivity to oxaliplatin: clinical features and risk factors. *BMC Pharmacol*
327 *Toxicol*. 2014;15(1):1.
- 328 17. Schwartz JR, Bandera C, Bradley A, Brard L, Legare R, Granai CO, et al. Does the
329 platinum-free interval predict the incidence or severity of hypersensitivity reactions to
330 carboplatin? The experience from Women and Infants' Hospital. *Gynecol Oncol*. 2007
331 Apr;105(1):81–3.
- 332 18. Sugimoto H, Iwamoto T, Murashima Y, Tabata T, Sagawa N, Okuda M. Risk factors
333 contributing to the development of carboplatin-related delayed hypersensitivity reactions
334 in Japanese patients with gynecologic cancers. *Cancer Chemother Pharmacol*. 2011
335 Feb;67(2):415–9.
- 336 19. Joly F, Ray-Coquard I, Fabbro M, Donoghoe M, Boman K, Sugimoto A, et al.
337 Decreased hypersensitivity reactions with carboplatin-pegylated liposomal doxorubicin
338 compared to carboplatin-paclitaxel combination: analysis from the GCIG CALYPSO
339 relapsing ovarian cancer trial. *Gynecol Oncol*. 2011 Aug;122(2):226–32.
- 340 20. Newman Taylor AJ, Cullinan P, Lympny PA, Harris JM, Dowdeswell RJ, du Bois RM.
341 Interaction of HLA phenotype and exposure intensity in sensitization to complex
342 platinum salts. *Am J Respir Crit Care Med*. 1999 Aug;160(2):435–8.
- 343 21. Seki K, Tsuduki Y, Ioroi T, Yamane M, Yamauchi H, Shiraishi Y, et al. Serum Lactate
344 Dehydrogenase Levels as a Predictive Marker of Oxaliplatin-Induced Hypersensitivity
345 Reactions in Japanese Patients with Advanced Colorectal Cancer. *Int J Med Sci*.
346 2014;11(6):641–5.

- 347 22. Leguy-Seguin V, Jolimoy G, Coudert B, Pernot C, Dalac S, Vabres P, et al. Diagnostic
348 and predictive value of skin testing in platinum salt hypersensitivity. *J Allergy Clin*
349 *Immunol.* 2007 Mar;119(3):726–30.
- 350 23. Markman M, Zanotti K, Peterson G, Kulp B, Webster K, Belinson J. Expanded
351 experience with an intradermal skin test to predict for the presence or absence of
352 carboplatin hypersensitivity. *J Clin Oncol Off J Am Soc Clin Oncol.* 2003 Dec
353 15;21(24):4611–4.
- 354 24. Zanotti KM, Rybicki LA, Kennedy AW, Belinson JL, Webster KD, Kulp B, et al.
355 Carboplatin skin testing: a skin-testing protocol for predicting hypersensitivity to
356 carboplatin chemotherapy. *J Clin Oncol Off J Am Soc Clin Oncol.* 2001 Jun
357 15;19(12):3126–9.
- 358 25. Lax T, Long A, Banerji A. Skin Testing in the Evaluation and Management of
359 Carboplatin-Related Hypersensitivity Reactions. *J Allergy Clin Immunol Pract.* 2015
360 Dec;3(6):856–62.
- 361 26. Dizon DS, Sabbatini PJ, Aghajanian C, Hensley ML, Spriggs DR. Analysis of patients
362 with epithelial ovarian cancer or fallopian tube carcinoma retreated with cisplatin after
363 the development of a carboplatin allergy. *Gynecol Oncol.* 2002 Mar;84(3):378–82.
- 364 27. Callahan MB, Lachance JA, Stone RL, Kelsey J, Rice LW, Jazaeri AA. Use of cisplatin
365 without desensitization after carboplatin hypersensitivity reaction in epithelial ovarian
366 and primary peritoneal cancer. *Am J Obstet Gynecol.* 2007 Aug;197(2):199.e1-4;
367 discussion 199.e4-5.
- 368 28. Elligers KT, Davies M, Sanchis D, Ferencz T, Saif MW. Rechallenge with cisplatin in a
369 patient with pancreatic cancer who developed a hypersensitivity reaction to oxaliplatin.
370 Is skin test useful in this setting. *JOP J Pancreas Online.* 2008;9(2):197–202.
- 371 29. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al.
372 Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid
373 desensitization in 413 cases. *J Allergy Clin Immunol.* 2008 Sep;122(3):574–80.
- 374 30. Barbaud A, Gonçalo M, Bruynzeel D, Bircher A. Guidelines for performing skin tests
375 with drugs in the investigation of cutaneous adverse drug reactions. *Contact Dermatitis.*
376 2001 Dec 1;45(6):321–8.
- 377 31. Brown SGA. Clinical features and severity grading of anaphylaxis. *J Allergy Clin*
378 *Immunol.* 2004 Aug;114(2):371–6.
- 379 32. Hunter D, Milton R, Perry KM. Asthma caused by the complex salts of platinum. *Br J*
380 *Ind Med.* 1945;2(2):92.

- 381 33. Greene DP, Ferriss JS, Jazaeri AA. Cisplatin administration following carboplatin
382 desensitization failure in primary peritoneal cancer: a brief report. *Cancer Chemother*
383 *Pharmacol.* 2010 Jul;66(2):265–7.
- 384 34. Li Q, Cohn D, Waller A, Backes F, Copeland L, Fowler J, et al. Outpatient rapid 4-step
385 desensitization for gynecologic oncology patients with mild to low-risk, moderate
386 hypersensitivity reactions to carboplatin/cisplatin. *Gynecol Oncol.* 2014 Oct;135(1):90–
387 4.
- 388 35. Caiado J, Castells M. Presentation and Diagnosis of Hypersensitivity to Platinum Drugs.
389 *Curr Allergy Asthma Rep* [Internet]. 2015 Apr [cited 2016 Apr 18];15(4). Available
390 from: <http://link.springer.com/10.1007/s11882-015-0515-3>
- 391 36. Enrique E, Malek T, Castelló JV, De Mateo JA. Usefulness of skin testing with platinum
392 salts to demonstrate lack of cross-reactivity between carboplatin and cisplatin. *Ann*
393 *Allergy Asthma Immunol.* 2008;100(1):86.
- 394 37. Brault F, Waton J, Poreaux C, Schmutz J-L, Barbaud A. [Hypersensitivity to platinum
395 salts and taxanes: The value of skin tests and tolerance induction procedures]. *Ann*
396 *Dermatol Venereol.* 2017 Nov;144(11):685–95.
- 397 38. Caiado J, Venemalm L, Pereira-Santos MC, Costa L, Barbosa MP, Castells M.
398 Carboplatin-, oxaliplatin-, and cisplatin-specific IgE: cross-reactivity and value in the
399 diagnosis of carboplatin and oxaliplatin allergy. *J Allergy Clin Immunol Pract.* 2013
400 Oct;1(5):494–500.
- 401 39. Kolomeyevskaya NV, Lele SB, Miller A, Riebandt GC, Blum BL, Odunsi KO, et al.
402 Oxaliplatin is a safe alternative option for patients with recurrent gynecologic cancers
403 after hypersensitivity reaction to Carboplatin. *Int J Gynecol Cancer Off J Int Gynecol*
404 *Cancer Soc.* 2015 Jan;25(1):42–8.
- 405 40. Syrigou E, Makrilia N, Vassias A, Nikolaidis I, Xyla V, Manolopoulos L, et al.
406 Administration of cisplatin in three patients with carboplatin hypersensitivity: is skin
407 testing useful? *Anticancer Drugs.* 2010 Mar;21(3):333–8.
- 408 41. Kandel MJ, Loehr A, Harter P, Traut A, Gnauert K, du Bois A. Cisplatinum rechallenge
409 in relapsed ovarian cancer patients with platinum reinduction therapy and carboplatin
410 hypersensitivity. *Int J Gynecol Cancer Off J Int Gynecol Cancer Soc.* 2005
411 Oct;15(5):780–4.
- 412 42. Libra M, Sorio R, Buonadonna A, Berretta M, Stefanovski P, Toffoli G, et al. Cisplatin
413 may be a valid alternative approach in ovarian carcinoma with carboplatin
414 hypersensitivity. Report of three cases. *Tumori.* 2003 Jun;89(3):311–3.

- 415 43. Porzio G, Marchetti P, Paris I, Narducci F, Ricevuto E, Ficorella C. Hypersensitivity
416 reaction to carboplatin: successful resolution by replacement with cisplatin. *Eur J*
417 *Gynaecol Oncol.* 2002;23(4):335–6.
- 418 44. Weidmann B, Mülleneisen N, Bojko P, Niederle N. Hypersensitivity reactions to
419 carboplatin. Report of two patients, review of the literature, and discussion of diagnostic
420 procedures and management. *Cancer.* 1994 Apr 15;73(8):2218–22.
- 421 45. Bergamini A, Pisano C, Di Napoli M, Arenare L, Della Pepa C, Tambaro R, et al.
422 Cisplatin can be safely administered to ovarian cancer patients with hypersensitivity to
423 carboplatin. *Gynecol Oncol.* 2017 Jan;144(1):72–6.
- 424 46. Polyzos A, Tsavaris N, Kosmas C, Arnaouti T, Kalahanis N, Tsigris C, et al.
425 Hypersensitivity reactions to carboplatin administration are common but not always
426 severe: a 10-year experience. *Oncology.* 2001;61(2):129–33.
- 427 47. Zweizig S, Roman LD, Muderspach LI. Death from anaphylaxis to cisplatin: a case
428 report. *Gynecol Oncol.* 1994 Apr;53(1):121–2.
- 429 48. Shlebak AA, Clark PI, Green JA. Hypersensitivity and cross-reactivity to cisplatin and
430 analogues. *Cancer Chemother Pharmacol.* 1995;35(4):349–51.
- 431 49. Ottaiano A, Tambaro R, Greggi S, Prato R, Di Maio M, Esposito G, et al. Safety of
432 cisplatin after severe hypersensitivity reactions to carboplatin in patients with recurrent
433 ovarian carcinoma. *Anticancer Res.* 2003 Aug;23(4):3465–8.
- 434 50. Giavina-Bianchi P, Patil SU, Banerji A. Immediate Hypersensitivity Reaction to
435 Chemotherapeutic Agents. *J Allergy Clin Immunol Pract.* 2017 Jun;5(3):593–9.
- 436

Patients tested for PS at Dijon University Hospital from September 2002 to April 2016
n=184

Exclusion : n=29 (delayed reactions)

Immediate hypersensitivity reactions
n = 155

Tests PS +
n = 97

1 PS
n = 56

OX
n = 28

CA
n = 25

CI
n = 3

> 1 PS
n = 41

OX + CA
n = 38

CA + CI
n = 2

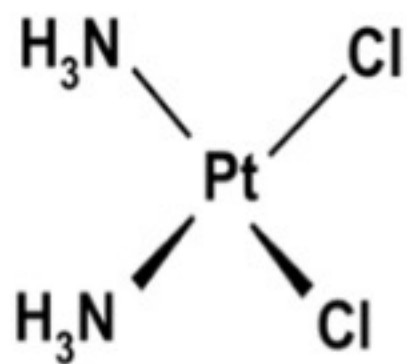
OX + CI
n = 0

OX + CA + CI
n = 1

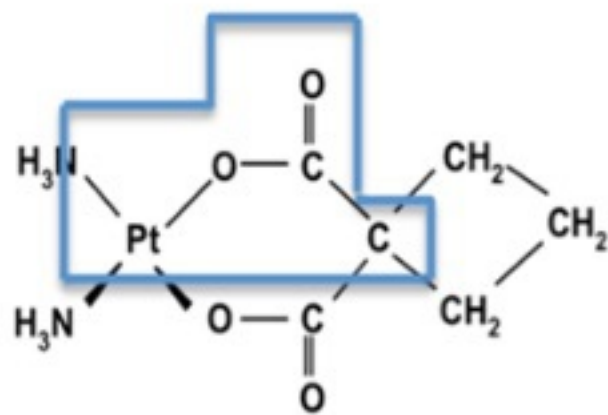
Tests PS -
n = 58

for all
n = 56

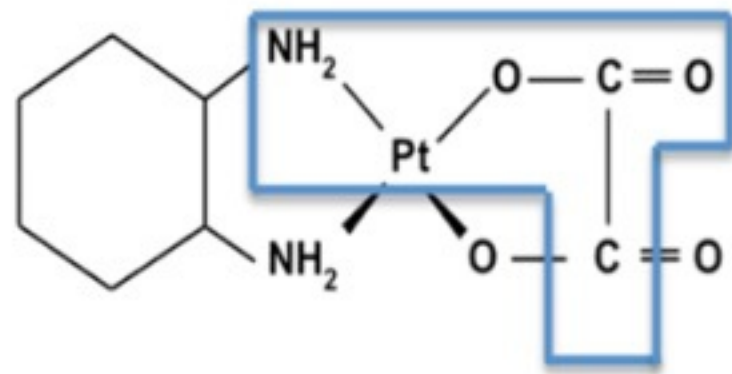
Concomittant
treatment
hypersensitivity
n = 2
Epirubicin
Ranitidine



a. cisplatin



b. carboplatin



c. oxaliplatin

N-Pt-O-CO-C chain

Table I. Baseline demographic characteristics of patients (n = 155)

Age, years	
Range	27-82
Mean	60.8
Median	60
Gender, no (%)	
Female	103 (66.4)
Male	52 (33.6)
Sex ratio	1.9
Tumor type, no (%)	
Colorectal	55 (35.5)
Ovarian	52 (33.6)
Pancreatic	14 (9)
Cholangiocarcinoma	6 (3.8)
Gastric	6 (3.8)
Pulmonary	6 (3.8)
Breast	4 (2.6)
Endometrial	4 (2.6)
Esophageal	3 (1.8)
Cervix	1 (0.7)
Fallopian tube	1 (0.7)
Peritoneal	1 (0.7)
Pharynx	1 (0.7)
Prostate	1 (0.7)

Table II. Clinical signs experimented during hypersensitivity reaction with platinum salts in the 155 patients.

Clinical signs	Patients, no (%)
Cutaneous (erythema, pruritus, urticaria, angioedema)	107 (69)
Cardiovascular (chest tightness, Tachycardia, blood pressure alterations)	47 (30)
Pulmonary (dyspnea, bronchospasm, desaturation)	18 (12)
Gastro-intestinal (nausea, vomiting, diarrhea)	13 (8)
Neurological (paresthesia, malaise, vertigo)	45 (29)

Table III. Results of positive IDTs: risk of cross-reactivity between the platinum salts (n=97)

Suspected PS with positive IDTs	IDTs results	Patients, no. (%)
Oxaliplatin n=51	OX alone	28 (55)
	OX + CA	23 (45)
	OX + CI	0 (0)
	OX + CA + CI	0 (0)
Carboplatin n=43	CA	25 (58)
	CA + OX	15 (35)
	CA + CI	2 (5)
	CA + CI + OX	1 (2)
Cisplatin n=3	CI alone	3 (100)
	CI + CA	0 (0)
	CI + OX	0 (0)
	CI + OX + CA	0 (0)

IDTs, Intradermal tests
OX, Oxaliplatin

CA, Carboplatin
CI, Cisplatin

Table IV. Re-administration of PS in patients with POSITIVE allergy testing (n=30)

Suspected PS		Results of PS administered		Hypersensitivity reaction	
		skin tests			
Cisplatin	n = 1	CI +	Carboplatin	n = 1	NO
Carboplatin	n = 9	CA +	Cisplatin	n = 6	NO
			Oxaliplatin	n = 3	NO
	n = 8	CA +, OX +	Cisplatin	n = 8	NO
Oxaliplatin	n = 7	OX +	Cisplatin	n = 6	NO
			Carboplatin	n = 1	NO
	n = 5	OX +, CA +	Cisplatin	n = 4	NO
			Oxaliplatin (desensitization)	n = 1	

PS, platinum salts; CA, carboplatin; OX, oxaliplatin; CI, cisplatin; + means positive skin test

Table V. Cisplatin rechallenge studies.

Study		Type of cancer	n	PS suspected	Successful, no (%)	Allergy, no (%)	Skin testing
Our study	2016	all types	33	Carboplatin Oxaliplatin	33 (100)	0	Yes
Bergamini et al.	2016	gynecological	38	Carboplatin	33 (86.8)	5 (13.2)	No
Kolomeyevskaya et al.	2015	gynecological	19	Carboplatin	19 (100)	0	No
Syrigou et al.	2010	ovarian, pulmonary	3	Carboplatin	3 (100)	0	Yes
Greene et al.	2009	gynecological	1	Carboplatin	1 (100)	0	No
Enrique et al.	2008	ovarian	2	Carboplatin	2 (100)	0	Yes
Elligers et al.	2008	pancreatic	1	Oxaliplatin	1 (100)	0	Yes
Callahan et al.	2007	gynecological	24	Carboplatin	18 (75)	6 (25)	No
Kandel et al.	2005	gynecological	5	Carboplatin	5 (100)	0	No
Libra et al.	2003	ovarian	3	Carboplatin	3 (100)	0	NA
Ottaiano et al.	2003	ovarian	10	Carboplatin	9 (90)	1 (10)	NA
Dizon et al.	2002	ovarian	7	Carboplatin	5 (71.4)	1 (14.3)	No
Porzio et al.	2002	ovarian	1	Carboplatin	1 (100)	0	Yes
Polygos et al.	2001	ovarian	4	Carboplatin	4 (100)	0	No
Shukunami et al.	1999	ovarian	1	Carboplatin	1 (100)	0	NA
Shelbak et al.	1995	ovarian	1	Carboplatin	0	1 (100)	No
Weidmann et al.	1994	ovarian, pancreatic	2	Carboplatin	2 (100)	0	No
Zweizig et al.	1994	ovarian	1	Carboplatin	0	0	No

NA, Not available; PS, Platinum Salt