

Presentation and Diagnosis of Hypersensitivity to Platinum Drugs

Joana Caiado · Mariana Castells

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Abstract Hypersensitivity reactions (HSRs) to platinum drugs are increasing due to their extensive use in a wide variety of malignancies and the repeated exposures in patients with increased life expectancy. Understanding the incidence of HSR to platinum drugs and associated risk factors can help with the diagnosis and may provide protection against severe HSRs. A thorough clinical history with identification of the typical and atypical symptoms, the relationship with the platinum administration, and the number of previous exposures are the key to the diagnosis. An elevated serum tryptase at the time of the HSR indicates that IgE and/or mast cells/basophils were involved in the HSR. Skin testing to platinum drugs is a highly sensitive and specific diagnostic tool, which helps provide risk stratification and management recommendations. Platinum specific IgE measurement and basophil activation test (BAT) are emerging as new diagnostic tools and in combination with skin testing can help support the diagnosis and the cross-reactivity between the three most commonly used platinum drugs, namely carboplatin, cisplatin, and oxaliplatin.

Keywords Chemotherapy · Platinum drugs · Carboplatin · Cisplatin · Oxaliplatin · Hypersensitivity · Allergy · Diagnosis · Skin test · IgE · Specific IgE · Basophil activation test

Introduction

Survival of cancer patients has increased in the last 10 years through improved medications and repeated courses of successful and targeted drugs [1]. Hypersensitivity reactions (HSRs), i.e., unexpected reactions which cannot be justified by the known toxicity profile of the drug [2], have been reported with most agents used for cancer chemotherapy [3]. Repeated exposures of the same drug leads to increased risk of hypersensitivity reactions (HSRs) [1, 3, 4], this being particularly true for platinum drugs since HSRs with these agents usually appear after multiple infusions [1, 3, 5–17].

There are three platinum salts most commonly used in cancer patients that can be administered in an outpatient setting due to their overall good safety profile. They share the same antineoplastic mechanism: their metabolites generate intra- and interstrand DNA adducts which lead to cell cycle arrest and apoptosis [18, 19].

Cisplatin is the first-generation platinum drug and was the first to be approved by FDA in 1978 [20], but it is being less prescribed due to its frequent side effects namely nephrotoxicity, neurotoxicity, ototoxicity, and the emetogenic potential [21, 22]. Nevertheless, it is still approved for testicular cancer [23] and head and neck malignancies [24].

Carboplatin is a second-generation platinum drug with much lower incidence of toxicity to the kidneys and the peripheral nervous system, and is widely used in place of cisplatin for gynecologic malignancies since 1979, in particular

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J. Caiado (✉)
Immunology Department, Hospital de Santa Maria, Centro
Hospitalar Lisboa Norte, Avenida Professor Egas Moniz,
1649-035 Lisbon, Portugal
e-mail: joanacaiado@hotmail.com

M. Castells
Division of Rheumatology, Immunology and Allergy, Department of
Medicine, Brigham and Women's Hospital, Harvard Medical School,
1 Jimmy Fund Way, Smith Building, Boston, MA 02115, USA
e-mail: mcastells@partners.org

for ovarian carcinoma [20]. It is also approved for lung [25] and bladder cancer [26] and for low-grade glioma in children [27].

Oxaliplatin, a third-generation platinum drug has been proven to be effective for colorectal cancer when used in different combinations (i.e., with capecitabine, bevacizumab, and other agents), but the most common combination is with 5-fluorouracil and leucovorin [28]. It was initially used as a rescue approach for metastatic colorectal cancer [29], but it is now approved as first-line treatment for metastatic and as adjuvant treatment for stage III colorectal cancer [30]. Besides colorectal cancer, oxaliplatin may be also indicated for gastric [31], testicular [32], or pancreatic malignancies [33].

Extensive literature provides evidence that recurrent treatments with carboplatin in patients with carboplatin-sensitive ovarian carcinoma increases the likelihood of HSRs [3, 6–8, 10, 11, 15, 34–38]. Colorectal cancer is currently the third more common cancer in western countries, and because oxaliplatin is a key chemotherapeutic agent, its increasing use also leads to increased HSRs [9, 14, 39–44]. HSRs to platinum drugs, when moderate to severe, may lead to drug discontinuation or substitution, and in particular for ovarian and colorectal cancers, the substitution for other less effective agents interferes with the prognosis of these patients [45].

Understanding the epidemiology, characteristic presentation, and diagnosis of HSRs to platinum drugs is critical for the management of patients who experience HSRs. Different management approaches have been developed to overcome HSRs, and rapid drug desensitization (RDD) has emerged as an effective treatment modality which allows the reintroduction of the culprit drug [1, 5, 7, 16, 35, 46–49] with increased safety and minimal side effects.

This review aims at outlining the epidemiology, clinical presentation, and diagnostic tools currently available for the diagnosis of HSRs to platinum drugs.

Incidence and Risk Factors for HSRs to Platinum Drugs

Platinum salts were first recognized as capable of inducing immediate HSRs in the 1970s in refinery workers who were continuously exposed to those compounds [50, 51]. With the extensive use of platinum drugs in a wide variety of malignancies, a significant increase of HSRs to these antineoplastic drugs has been observed in cancer-treated patients. The three most frequent platinum inducing HSR are cisplatin, carboplatin, and oxaliplatin.

Carboplatin is the platinum drug with more reports of HSR in the literature, especially due to its wide use as front-line therapy in ovarian cancer. Overall, carboplatin HSRs occur in 4.6 % of cancer patients [52], rising to 16 % when analyzing the population of ovarian cancer patients [12]. The incidence of HSRs to carboplatin in children with low-grade glioma is

even higher. A Turkish group reported an incidence of 40 % in a cohort of 50 patients [53], and in a Canadian multicenter study, which involved 105 children, the incidence reached 41.9 % [54]. HSRs to cisplatin exhibit similar incidence characteristics as for carboplatin [10, 11], although are now less frequent due to its lesser use. HSRs to oxaliplatin have been increasingly recognized, but the real incidence varies among several reports from 10.3 % (MOSAIC trial) [28] to 11.7–25 % [41, 44, 55–57]. The difficulty to evaluate its exact prevalence is due to the variability of its clinical presentation.

Several authors have tried to identify different risk factors that can contribute to the high incidence of HSRs to platinum drugs. Multiple and repeated exposures to carboplatin (and cisplatin) infusions are clearly the most important predictive factor for HSRs [3, 5–8, 11, 38, 58]. Most patients with carboplatin-sensitive ovarian cancer are initially treated with six carboplatin infusions every 3 weeks, and in case of a relapse occurring after a >6-month cancer-free interval, patients receive six more carboplatin infusions [59]. It is during this re-treatment setting that most HSRs occur [6, 7]. Markman initially recognized the need of previous exposures to carboplatin before the onset of a HSR [11], and since then multiple authors have acknowledged this observation [5–7, 12, 15, 17, 35, 36]. According to different reports, the risk of having a HSR to carboplatin before the 6th infusion is 0.92 % [11] increasing to 19 % [11, 38], 21.7 % [6], and 23.6 % [60••] during the first re-treatment setting. The risk continues to increase along with subsequent re-exposures, and there are reports of a risk of 44 % [58], 86.7 % [6], to 100 % [15] of developing a HSR to carboplatin in a third-line treatment after a second relapse.

For oxaliplatin, the allergic sensitization also requires repeated exposures. Patients usually react at a median during the 7th [9, 41] to the 9th infusion [44, 57], although Parel et al. [14] reported a median of 3 prior infusions before HSR onset. Wong et al. analyzed 48 patients who reacted to oxaliplatin and described two clusters of HSRs, the first around the 8–9th infusion and the second at the 13–14th infusion with no clear peak as seen for carboplatin [16]. In order to reduce neurotoxicity, there is now a new stop-and-go strategy in which patients are initially submitted to six cycles of oxaliplatin, and then the infusions are resumed at the time of disease progression. Mori et al. have shown that the incidence of HSRs to oxaliplatin increases from 7.1 % considering the first six cycles to 20.6 % when the patients receive more than six cycles administered every 2 weeks with no interruption and to 41 % after a platinum-free interval followed by second-line treatment once a relapse of the cancer disease occurs [56].

For oxaliplatin, the incidence of HSRs is higher during palliative second-line treatments (19.6–24 %) as compared to adjuvant treatments (9–10.2 %) [41, 57], in particular after a first regimen including irinotecan [57].

A high cumulative dose has been implicated as contributing to an increase of HSRs to carboplatin. Sugimoto et al.

reported that a maximum dose/body of >650 mg of carboplatin is an independent risk factor for HSRs [61], while Joly F et al could not corroborate this observation since in this large study, this trend was not identified [60••].

Age has been suggested as an independent variable for predicting HSR to carboplatin. Joly F et al. analyzed a large cohort of patients with relapsed ovarian cancer and older patients (>70 year old) had lower rates of HSR to carboplatin [60••]. Younger age has also been considered a risk factor for hypersensitivity to oxaliplatin [41].

The female gender has been reported to increase the risk of HSRs in children with LGG with a relative risk for HSR of 1.92 (95 % confidence interval, 1.12–3.30) [54]. Not surprisingly, this topic is not as frequently addressed for carboplatin HSRs in general, since the large epidemiologic studies have been performed with female patients with ovarian cancer. Females are also predominant (59–62 %) among patients who experience HSRs to oxaliplatin [14, 16, 44].

The schedule of the administration of carboplatin has been valued as a predictive factor, and most HSRs in children with low-grade glioma (LGG) occur with weekly as compared to monthly administration [53, 62], and Lafay-Cousin L. et al. also reported that HSRs occurred significantly earlier among children with LGG on weekly treatments [54].

A higher risk of sensitization to platinum drugs has also been associated with a longer platinum-free interval. In one study, patients with a platinum-free interval of <12 months had a risk of 25.8 % of having a HSR as opposed to a risk of 56.5 % when the platinum-free interval was ≥12 months [15]. In another study, a platinum-free interval of ≥23.4 months increased four-fold the likelihood of having a HSR upon re-exposure as compared with shorter intervals [6]. A longer platinum-free interval has also been associated with higher incidence of HSRs in patients undergoing the stop-and-go regimen for oxaliplatin [56].

Different combination regimens influence the rate of HSRs to carboplatin. A large trial involving 976 patients (GCIG CALYPSO relapsing ovarian cancer trial) showed that HSRs were less frequent in the regimens including carboplatin and pegylated liposomal doxorubicin (15.5 %) as compared with standard carboplatin–paclitaxel (33.1 %) in patients with platinum-sensitive relapsed ovarian cancer [60••]. For cisplatin, a predictive factor associated with an increase of HSRs is concomitant radiation, increasing the risk up to 16 % [63].

The role of atopy as risk factor for HSR to platinum drugs has been evaluated and Li Q et al. have identified an incidence of 44 % of atopy [64], higher than the one described in the general population of 20–30 % [65]. Markman et al. found a positive association with a higher risk of HSRs to carboplatin in patients with previous history of hypersensitivity to other drugs [66]. Castells et al. also observed that 56.1 % of patients who experienced reactions to antineoplastic agents had previous history of atopy, namely allergic rhinitis/conjunctivitis,

asthma, food allergies, urticaria, eczema, and/or latex allergy [5]. However, in a large cohort involving 976 patients with relapsed ovarian cancer, only 6 % of the patients experiencing HSRs had previous medical history of allergy [60••]. The incidence of atopic disease among patients allergic to oxaliplatin is similar to the one described for patients receiving oxaliplatin with no HSRs [14, 41, 56].

In a study involving 87 patients with recurrent gynecologic cancer, germline BRCA1/2 mutations were identified as an independent risk factors for carboplatin HSRs; these mutations were more frequent among patients who experienced any HSR to carboplatin (93 %) as compared with the patients with no HSRs (50 %) [67].

Previous treatment with a different platinum drug is considered a risk factor for developing a HSR to a different platinum drug. Few studies have shown that a platinum drug can be safely switched to another with or without desensitization [64, 68–71]; however, recurrent HSRs have been observed after the substitution of one platinum drug by another. Gaducci et al. showed that 22.2 % of the patients with previous HSRs to carboplatin also reacted to cisplatin upon challenge [6]. Similarly, Dizon et al. [72] and Zweizig et al. [73] reported severe HSRs after the substitution of carboplatin for cisplatin.

Meyer et al. have shown that in eight patients who had HSRs to oxaliplatin had also positive skin testing to carboplatin demonstrating sensitization to both platinum drugs, without carboplatin exposure [74]. However, Taylor et al., showed in a group of 44 patients previously treated with cisplatin and/or carboplatin for colon cancer and in whom 23 patients (52.3 %) had experienced HSRs that oxaliplatin treatment only induced one HSR in a patient manifested by back pain [75]. Rose et al. also reported that oxaliplatin desensitization can be tolerated by patients who had initial HSRs to carboplatin and were not able to tolerate the carboplatin desensitization previously [76].

Nedaplatin, a recent cisplatin analog has been investigated as an alternative for cisplatin/carboplatin in patients with previous HSRs. Michikami et al. showed in a group of 38 patients allergic to carboplatin that 7.9 % of the patients experienced HSRs to nedaplatin [77]. Arimoto et al. also identified 27 % of recurrent HSRs after the substitution of carboplatin for nedaplatin, and this substitution is not currently recommended [78]. To our knowledge, there are no reports of HSR induced by the new platinum drugs satraplatin or picoplatin.

Characteristics of HSRs to Platinum Drugs

Most of the HSRs induced by platinum drugs occur during or immediately after the drug administration and are classified as type I allergic reactions, with clinical symptoms consistent with the actions of mediators release from IgE and non-IgE

activated mast cells and basophils [79]. An IgE mechanism is supported by the immediate onset of the symptom during or shortly after the drug infusion, the need for multiple exposures for sensitization, a positive skin testing in reactive patients [5, 7, 8, 13, 16, 17, 35, 39, 80•, 81, 82•], and the detection of platinum-specific IgEs in platinum-sensitized patients [49, 83, 84]. Mast cell and/or basophil activation is supported by elevated tryptase, a major pre-formed serine protease that is released during an immediate reaction due to mast cell activation [85–87] and increases above normal range (>11.4 ng/ml) has been reported by Hesterberg et al. in patients who had breakthrough HSR during desensitization to carboplatin [7].

HSR type II has been reported with oxaliplatin such as immune thrombocytopenia and hemolytic anemia due to autoantibodies to erythrocytes and to platelets as a result of oxaliplatin adsorption on blood cells [88, 89]. Case series evaluating hypersensitivity to oxaliplatin have provided evidence of type II reactions attributed to oxaliplatin [9, 16, 44].

Type IV hypersensitivity to platinum drugs are rare, with few case reports [11, 90], but the real incidence may be underestimated. McAlpine et al. have shown that patients that experience a delayed reaction to carboplatin, namely a maculopapular rash, may be at risk of developing an immediate HSR in the following exposures [91].

An accurate diagnosis of HSR to platinum drugs is the most important step for an optimal management. A thorough clinical history with the identification of the drug at the time of the HSR, the quantification of previous exposures, and the characteristics of the reaction are important. When two drugs are infused sequentially, it may be difficult to identify the culprit medication. In carboplatin-based regimens, paclitaxel is infused before carboplatin and can be responsible for the HSRs. Some features are more suggestive of taxanes HSRs which occur typically during the 1st or 2nd infusions and present with atypical symptoms such as thoracic, abdominal, or back pain [5, 11, 92–94]. Before establishing the diagnosis, other potential causes for the clinical symptoms need to be excluded such as other drugs that patients may have taken at home, a food allergy, or an underlying infectious disease [4].

According to the NCI-CTAE [95], HSRs are classified from 1 to 5: 1 and 2 include transient flushing or rash, drug fever needing no intervention, or prompt response to symptomatic treatment and are usually considered mild; 3 and 4 include symptomatic bronchospasm, with or without urticaria, allergy-related edema/angioedema, and hypotension requiring urgent parenteral intervention and are thus considered severe, and 5 is death. The Brown's classification is consistent with mild HSRs (grade 1) when there is only cutaneous/subcutaneous involvement, moderate (grade 2) when features suggesting respiratory, cardiovascular, or gastrointestinal involvement are present, and severe (grade 3) when hypoxia, asphyxia, hypotension, or neurologic compromise is observed [96]. Based on the two classifications, most of the HSRs to

platinum drugs are classified as mild (Table 1), but several studies found 50 % of moderate to severe HSRs to carboplatin [3, 11].

Oxaliplatin HSRs are often referred as being milder than for carboplatin, but several reports indicate that 1.5–9 % are severe reactions [28, 41, 44, 57] with anaphylactic HSRs and deaths have been reported [76–78].

In terms of clinical presentation, the most frequent and early symptoms/signs are cutaneous including palmar pruritus and erythema, flushing, or rash [11] for all three platinum drugs (Table 1). Respiratory symptoms are the second more frequent clinical presentation, being slightly higher for oxaliplatin, with reports of dyspnea and hypoxia with no associated bronchospasm [41]. Cardiovascular symptoms are the most severe and still frequent HSRs, reaching 50 % of all reactions in some case series (Table 1). Pain is reported as a HSR but is not as frequent as it is for taxanes [5, 94].

In the last years, there have been increasing reports of atypical symptoms such as chills/rigors, fever, and abdominal and/or severe chest pain during the infusion of oxaliplatin [10, 13, 14, 16, 39–41, 47, 49, 100, 101], reaching 33.3 % of all reported symptoms [9]. These have been considered non-immune-mediated reaction and may be consistent with idiosyncratic reactions due to a cytokines storm (IL-1b, IL-6, TNF- α) [101, 102]. It has been hypothesized that oxaliplatin can bind to mononuclear cells and act as a superantigen with subsequent cytokine release [103]. In addition, mast cells mediated cytokine release could contribute through the secretions of pyrogenic cytokines (IL-1 β , IL-6, TNF- α). The management of these reactions is similar to other immediate HSRs and desensitization, with or without premedication with NSAIDs has proven to overcome these reactions [16, 100]. When atypical symptoms such as fever and chills occur during oxaliplatin infusion, coincidental with the manipulation of an implantable port, an infection of the central catheter needs to be excluded.

Another atypical symptoms related to oxaliplatin is dysesthesia with laryngeal spasm, a neurotoxic effect that is often manifested by stridor; it can happen during the infusion or several hours later and should be differentiated from a true HSR [104].

Diagnosis of HSRs to Platinum Drugs

Skin testing (ST) has proven to be helpful in the evaluation of IgE-mediated HSR to a platinum drug. The sensitivity of ST to platinum drugs varies among several studies and a sensitivity of 66 % [7, 8] has been found when using 1 mg/ml as maximum concentration in reactive patients. Lee et al. [36, 81] and Castells et al. [5] found higher sensitivity (80–88 %) in 91 patients with previous reactions to carboplatin with 10 mg/ml in intradermal testing. Confino-Cohen et al. skin

Table 1 Comparison of the epidemiology, risk factors, clinical presentation, and skin testing to cisplatin, carboplatin, and oxaliplatin

	Cisplatin	Carboplatin	Oxaliplatin
Incidence	[10, 11]	[5, 10, 11, 41, 53, 54, 58]	[28, 41, 44, 55, 56]
Overall	5–16%	≈5%	≈10%
≥7 infusions	NA	19–27%	20.6–41%
≥13 infusions	NA	44–100%	NA
Risk factors	[63]	[5–7, 58, 61, 62, 66, 67]	[28, 42, 44, 55, 56, 97]
Multiple previous exposures	+	+	+/-
Female gender	+	+	+/-
Younger age	NA	+	+
High cumulative dose	NA	+	+
Atopy/drug allergy	NA	+/-	+/-
Long platinum-free interval	NA	+	+
Others	Concomitant radiation	BRCA1/2 mutations, weekly administration	Previous regimens with irinotecan
Clinical presentation	[5]	[5, 6, 98]	[9, 16, 44, 97]
Cutaneous symptoms (pruritus, flushing, urticaria)	67%	86.7–100%	41–82.3%
Respiratory symptoms (cough, dyspnea, bronchospasm)	–	8.7–40%	35–53%
Gastrointestinal symptoms (nausea, vomiting)	–	2.9–30%	19–29%
Cardiovascular symptoms (hypertension, hypotension)	67%	4.3–57%	7–33%
Pain (thoracic, back, or abdominal)	–	1.7–5%	5.8–6%
Oropharyngeal	–	25%	6%
Neurologic	–	15–40%	5%
Systemic/idiosyncratic (fever, diaphoresis, chills, rigors)	–	–	11–33.3%
Severity of the HSRs (NCI-CTAE)	[97]	[6, 11, 53, 94, 99]	[41, 44, 97, 99]
Mild (grade 1–2)	53%	46–75 %	41.1–88.1%
Severe (grade 3–5)	47%	25–54 %	11.9–53%
Skin testing	[5, 8]	[5, 7, 8, 17, 35, 36, 66, 81, 82••]	[8, 16, 39, 40, 43, 49]
Concentrations (ID)	1 mg/ml	1–10 mg/ml	1–5 mg/ml
Sensitivity	66.7%	66–100%	26–100%
Positive predictive value	NA	94–98.5%	95%

(+): presence of the analyzed item; (–): absence of the analyzed item; (+/-): not consensual among all authors

NA information not available, ID intradermal, NCI-CTAE National Cancer Institute-Common Terminology for Adverse Events

tested 23 patients with moderate to severe HSRs to carboplatin and showed that all patients had positive skin testing (100 % sensitivity), hypothesizing that the sensitivity of the ST may be related to the severity of the initial HSR [35].

The sensitivity of oxaliplatin ST varies according to different studies from 26 to 100 % [8, 16, 39, 40, 43, 49]. Wong et al. have demonstrated that patients with positive skin testing to oxaliplatin are more likely to have breakthrough HSRs during the desensitization procedure as compared with negative ST [16].

Carboplatin and oxaliplatin, when used at high concentrations (10 and 5 mg/ml, respectively), may induce an irritant

reaction characterized by local pruritus/pain, redness, and sometimes delayed local cutaneous necrosis usually reversible with local steroids [7, 43, 84], although some authors have used the same concentrations with no adverse effects [5, 16, 39, 40, 49, 81, 84]. For cisplatin, the non-irritant concentration is 0.1–1 mg/ml for IDT [5, 8, 105]. The results of skin testing of patients with remote HSRs to platinum drugs should be carefully evaluated. According to a study by Patil et al. [82••], 52 % of the patients with remote HSRs and negative skin testing converted to having positive skin after two desensitizations to carboplatin, being thus considered false negatives. The authors also showed that these converters have an

increased risk of having breakthrough HSRs during the desensitization procedures (83.3 %).

Due to its high specificity, ST has been performed after the sixth cycle of carboplatin to evaluate cutaneous sensitization [8, 17, 80•] with 94–98.5 % negative predictive values. Pagani et al. [13] have also prospectively evaluated ST reactivity to oxaliplatin and found a negative predictive value of 95 % (5 % false negatives). For patients with positive skin test when there is no first-line alternative, desensitization is a treatment option [1]. Cross-reactivity between platinum drugs can be assessed with ST [72, 73]. A negative ST to the alternative platinum drug has an elevated negative predictive value allowing to safely reintroduce a different platinum drug when no other chemotherapeutic agent seems to be as effective [8, 68, 69, 71]. Patch testing in reactive platinum patients has not been of predictive value [8] and is not recommended.

Other diagnostic tools are being investigated since ST may induce local irritation and rarely anaphylactic reactions [106]. Specific IgE (sIgE) in vitro evaluation using the ImmunoCAP system (ThermoFisher™) [49, 83, 84] has shown encouraging results. Pagani et al. [83] initially reported the detection of carboplatin-sIgE in 3/3 patients with a positive history of HSR to carboplatin. The value of platinum-sIgE in 24 patients with moderate to severe HSRs (12 carboplatin/12 oxaliplatin) and 17 controls (exposed but with no HSR) [84] showed a higher sensitivity for oxaliplatin (75 %) than for carboplatin (58.3 %), although the sIgE to carboplatin was more specific (100 %) in the study of Caiado et al. In this study, 89 % of the patients exposed to oxaliplatin alone had also detectable sIgE to the other two platinum drugs. These results indicate that sIgE determination can be a helpful tool for the diagnosis. Madrigal-Burgaleta et al. quantified oxaliplatin-sIgE in 13 oxaliplatin-reactive patients and showed a sensitivity of 38–54 % but the severity of the HSRs had a wide range.

Basophil activation test (BAT) has been used to identify carboplatin HSRs. Iwamoto et al. showed that basophils increased the expression of CD203c when incubated with carboplatin in patients with grade 2–4 HSR to carboplatin [107••]. Validation will be required in future studies for the specificity and sensitivity of the BAT for platins since there is a paucity of data regarding patients receiving multiple courses and not developing allergic reactions.

Conclusions

HSRs are being increasingly reported with platinum drugs in parallel with the higher longevity of cancer patients. Because of the longer survival, patients are exposed to larger amounts of platinum drugs which is a risk factor for HSRs. Other risk factors include younger age, female gender, and a longer platinum-free interval between the different lines of treatment and atopy, including drug allergy. In the acute setting, serum

tryptase should be measured to confirm anaphylaxis. Skin testing is the most frequently used diagnostic test with high sensitivity and specificity and can help to determine cross-reactivity among the three platins. Other diagnostic tools have been investigated such as platinum-sIgE and BAT both aimed at assessing HSR in patients who cannot undergo skin testing and to determine cross-reactivity. Improvements of these assays will allow, in the near future, their widespread use in clinical practice.

Compliance with Ethics Guidelines

Conflict of Interest D. Joana Caiado declares a grant from Fundação Luso-Americana para o Desenvolvimento (FLAD.) Mariana Castells reports personal fees from Merck and Sanofi, personal fees from BWH, grants from NIH Desensitization, personal fees from UpToDate, and other from AAAAIBOD.

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References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Liu A, Fanning L, Chong H, Fernandez J, Sloane D, Sancho-Serra M, et al. Desensitization regimens for drug allergy: state of the art in the 21st century. *Clin Exp Allergy*. 2011;41(12):1679–89.
2. Shepherd GM. Hypersensitivity reactions to chemotherapeutic drugs. *Clin Rev Allergy Immunol*. 2003;24(3):253–62.
3. Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist*. 2007;12(5):601–9.
4. Khan DA, Solensky R. Drug allergy. *J Allergy Clin Immunol*. 2010;125(2 Suppl 2):S126–37.
5. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol*. 2008;122(3):574–80.
6. Gadducci A, Tana R, Teti G, Zanca G, Fanucchi A, Genazzani AR. Analysis of the pattern of hypersensitivity reactions in patients receiving carboplatin retreatment for recurrent ovarian cancer. *Int J Gynecol cancer*. 2008;18(4):615–20.
7. Hesterberg PE, Banerji A, Oren E, Penson RT, Krasner CN, Seiden MV, et al. Risk stratification for desensitization of patients with carboplatin hypersensitivity: clinical presentation and management. *J Allergy Clin Immunol*. 2009;123(6):1262–7 e1.
8. Leguy-Seguin V, Jolimoy G, Coudert B, Pernot C, Dalac S, Vabres P, et al. Diagnostic and predictive value of skin testing in platinum salt hypersensitivity. *J Allergy Clin Immunol*. 2007;119(3):726–30.
9. Maindrault-Goebel F, Andre T, Tournigand C, Louvet C, Perez-Staub N, Zeghib N, et al. Allergic-type reactions to oxaliplatin:

- retrospective analysis of 42 patients. *Eur J Cancer*. 2005;41(15):2262–7.
10. Makrilia N, Syrigou E, Kaklamanos I, Manolopoulos L, Saif MW. Hypersensitivity reactions associated with platinum antineoplastic agents: a systematic review. *Metal-Based Drugs*. 2010;2010.
 11. Markman M, Kennedy A, Webster K, Elson P, Peterson G, Kulp B, et al. Clinical features of hypersensitivity reactions to carboplatin. *J Clin Oncol*. 1999;17(4):1141.
 12. Navo M, Kunthur A, Badell ML, Coffey LW, Markman M, Brown J, et al. Evaluation of the incidence of carboplatin hypersensitivity reactions in cancer patients. *Gynecol Oncol*. 2006;103(2):608–13.
 13. Pagani M, Bonadonna P. Skin test protocol for the prevention of hypersensitivity reactions to oxaliplatin. *Anticancer Res*. 2014;34(1):537–40.
 14. Parel M, Ranchon F, Nosbaum A, You B, Vantard N, Schwietz V, et al. Hypersensitivity to oxaliplatin: clinical features and risk factors. *BMC Pharmacol Toxicol*. 2014;15:1.
 15. Schwartz JR, Bandera C, Bradley A, Brard L, Legare R, Granai CO, et al. Does the platinum-free interval predict the incidence or severity of hypersensitivity reactions to carboplatin? The experience from Women and Infants' Hospital. *Gynecol Oncol*. 2007;105(1):81–3.
 16. Wong JT, Ling M, Patil S, Banerji A, Long A. Oxaliplatin hypersensitivity: evaluation, implications of skin testing, and desensitization. *J All Clin Immunol Pract*. 2014;2(1):40–5.
 17. Zanotti KM, Rybicki LA, Kennedy AW, Belinson JL, Webster KD, Kulp B, et al. Carboplatin skin testing: a skin-testing protocol for predicting hypersensitivity to carboplatin chemotherapy. *J Clin Oncol*. 2001;19(12):3126–9.
 18. Raymond E, Faivre S, Woyanowski JM, Chaney SG. Oxaliplatin: mechanism of action and antineoplastic activity. *Semin Oncol*. 1998;25(2 Suppl 5):4–12.
 19. Kelland L. The resurgence of platinum-based cancer chemotherapy. *Nat Rev Cancer*. 2007;7(8):573–84.
 20. Monneret C. Platinum anticancer drugs. From serendipity to rational design. *Ann Pharm Fr*. 2011;69(6):286–95.
 21. Sakaeda T, Kadoyama K, Okuno Y. Adverse event profiles of platinum agents: data mining of the public version of the FDA adverse event reporting system, AERS, and reproducibility of clinical observations. *Int J Med Sci*. 2011;8(6):487–91.
 22. Sprauten M, Darrah TH, Peterson DR, Campbell ME, Hannigan RE, Cvancarova M, et al. Impact of long-term serum platinum concentrations on neuro- and ototoxicity in cisplatin-treated survivors of testicular cancer. *J Clin Oncol*. 2012;30(3):300–7.
 23. Haugnes HS, Bosl GJ, Boer H, Gietema JA, Brydoy M, Oldenburg J, et al. Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up. *J Clin Oncol*. 2012;30(30):3752–63.
 24. Geiger JL, Lazim AF, Walsh FJ, Foote RL, Moore EJ, Okuno SH, et al. Adjuvant chemoradiation therapy with high-dose versus weekly cisplatin for resected, locally-advanced HPV/p16-positive and negative head and neck squamous cell carcinoma. *Oral oncology*. 2014.
 25. Cohen MH, Gootenberg J, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) plus carboplatin and Paclitaxel as first-line treatment of advanced/metastatic recurrent nonsquamous non-small cell lung cancer. *Oncologist*. 2007;12(6):713–8.
 26. Yoneyama T, Tobisawa Y, Yoneyama T, Yamamoto H, Imai A, Hatakeyama S, et al. Carboplatin-based combination chemotherapy for elderly patients with advanced bladder cancer. *Int J Clin Oncol*. 2014. doi:10.1007/s10147-014-0706-2.
 27. Jakacki RI, Bouffet E, Adamson PC, Pollack IF, Ingle AM, Voss SD, et al. A phase I study of vinblastine in combination with carboplatin for children with low-grade gliomas: a Children's Oncology Group phase I consortium study. *Neuro-Oncology*. 2011;13(8):910–5.
 28. Andre T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med*. 2004;350(23):2343–51.
 29. Rothenberg ML, Oza AM, Bigelow RH, Berlin JD, Marshall JL, Ramanathan RK, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. *J Clin Oncol*. 2003;21(11):2059–69.
 30. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol*. 2009;27(19):3109–16.
 31. Li J, Yao X, Kortmansky JS, Fischbach NA, Stein S, Deng Y, et al. Phase II study of modified FOLFOX6 with bevacizumab in metastatic gastroesophageal adenocarcinoma. *Am J Clin Oncol*. 2014. doi:10.1097/COC.000000000000114.
 32. Uchida M, Kawai K, Kimura T, Ichioka D, Takaoka EI, Suetomi T, et al. Salvage chemotherapy with gemcitabine plus oxaliplatin for patients with testicular germ cell cancer. *Int J Clin Oncol*. 2014;19(6):1112–7.
 33. Lee MG, Lee SH, Lee SJ, Lee YS, Hwang JH, Ryu JK, et al. 5-Fluorouracil/leucovorin combined with irinotecan and oxaliplatin (FOLFIRINOX) as second-line chemotherapy in patients with advanced pancreatic cancer who have progressed on gemcitabine-based therapy. *Chemotherapy*. 2013;59(4):273–9.
 34. Castells M. Rapid desensitization of hypersensitivity reactions to chemotherapy agents. *Curr Drug Safety*. 2006;1(3):243–51.
 35. Confino-Cohen R, Fishman A, Altaras M, Goldberg A. Successful carboplatin desensitization in patients with proven carboplatin allergy. *Cancer*. 2005;104(3):640–3.
 36. Lee CW, Matulonis UA, Castells MC. Carboplatin hypersensitivity: a 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. *Gynecol Oncol*. 2004;95(2):370–6.
 37. Markman M. The dilemma of carboplatin-associated hypersensitivity reactions in ovarian cancer management. *Gynecol Oncol*. 2007;107(2):163–5.
 38. Sliesoraitis S, Chikhale PJ. Carboplatin hypersensitivity. *Int J Gynecol Cancer*. 2005;15(1):13–8.
 39. Garufi C, Cristaudo A, Vanni B, Bria E, Aschelter AM, Santucci B, et al. Skin testing and hypersensitivity reactions to oxaliplatin. *Ann Oncol*. 2003;14(3):497–8.
 40. Herrero T, Tomero P, Infante S, Fuentes V, Sanchez MN, De Barrio M, et al. Diagnosis and management of hypersensitivity reactions caused by oxaliplatin. *J Investig Allergol Clin Immunol*. 2006;16(5):327–30.
 41. Kim BH, Bradley T, Tai J, Budman DR. Hypersensitivity to oxaliplatin: an investigation of incidence and risk factors, and literature review. *Oncology*. 2009;76(4):231–8.
 42. Kim MY, Kang SY, Lee SY, Yang MS, Kim MH, Song WJ, et al. Hypersensitivity reactions to oxaliplatin: clinical features and risk factors in Koreans. *Asian Pac J Cancer Prevention : APJCP*. 2012;13(4):1209–15.
 43. Pagani M, Bonadonna P, Senna GE, Antico A. Standardization of skin tests for diagnosis and prevention of hypersensitivity reactions to oxaliplatin. *Int Arch Allergy Immunol*. 2008;145(1):54–7.

44. Polyzos A, Tsavaris N, Gogas H, Souglakos J, Vambakas L, Vardakas N, et al. Clinical features of hypersensitivity reactions to oxaliplatin: a 10-year experience. *Oncology*. 2009;76(1):36–41.
45. Mezzano V, Giavina-Bianchi P, Picard M, Caiado J, Castells M. Drug desensitization in the management of hypersensitivity reactions to monoclonal antibodies and chemotherapy. *BioDrugs*. 2014;28(2):133–44.
46. Castells M. Rapid desensitization for hypersensitivity reactions to chemotherapy agents. *Curr Opin Allergy Clin Immunol*. 2006;6(4):271–7.
47. Gastaminza G, de la Borbolla JM, Goikoetxea MJ, Escudero R, Anton J, Espinos J, et al. A new rapid desensitization protocol for chemotherapy agents. *J Investig Allergol Clin Immunol*. 2011;21(2):108–12.
48. Limsuwan T, Castells MC. Outcomes and safety of rapid desensitization for chemotherapy hypersensitivity. *Expert Opin Drug Saf*. 2010;9(1):39–53.
49. Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, Ferreira-Monteagudo R, Guillen-Ponce C, Pueyo C, et al. Hypersensitivity and desensitization to antineoplastic agents: outcomes of 189 procedures with a new short protocol and novel diagnostic tools assessment. *Allergy*. 2013;68(7):853–61.
50. Cleare MJ, Hughes EG, Jacoby B, Pepys J. Immediate (type I) allergic responses to platinum compounds. *Clin Allergy*. 1976;6(2):183–95.
51. Cromwell O, Pepys J, Parish WE, Hughes EG. Specific IgE antibodies to platinum salts in sensitized workers. *Clin Allergy*. 1979;9(2):109–17.
52. Demoor PA, Matusov Y, Kelly C, Kolan S, Barnachea L, Bazhenova LA. A retrospective review of the frequency and nature of acute hypersensitivity reactions at a medium-sized infusion center: comparison to reported values and inconsistencies found in literature. *J Cancer*. 2011;2:153–64.
53. Genc DB, Canpolat C, Berrak SG. Clinical features and management of carboplatin-related hypersensitivity reactions in pediatric low-grade glioma. *Support Care Cancer*. 2012;20(2):385–93.
54. Lafay-Cousin L, Sung L, Carret AS, Hukin J, Wilson B, Johnston DL, et al. Carboplatin hypersensitivity reaction in pediatric patients with low-grade glioma: a Canadian Pediatric Brain Tumor Consortium experience. *Cancer*. 2008;112(4):892–9.
55. Shao YY, Hu FC, Liang JT, Chiu WT, Cheng AL, Yang CH. Characteristics and risk factors of oxaliplatin-related hypersensitivity reactions. *J Formos Med Assoc*. 2010;109(5):362–8.
56. Mori Y, Nishimura T, Kitano T, Yoshimura K, Matsumoto S, Kanai M, et al. Oxaliplatin-free interval as a risk factor for hypersensitivity reaction among colorectal cancer patients treated with FOLFOX. *Oncology*. 2010;79(1–2):136–43.
57. Siu SW, Chan RT, Au GK. Hypersensitivity reactions to oxaliplatin: experience in a single institute. *Ann Oncol*. 2006;17(2):259–61.
58. Morgan JS, Adams M, Mason MD. Hypersensitivity reactions to carboplatin given to patients with relapsed ovarian carcinoma. *Eur J Cancer*. 1994;30A(8):1205–6.
59. Raja FA, Counsell N, Colombo N, Pfisterer J, du Bois A, Parmar MK, et al. Platinum versus platinum-combination chemotherapy in platinum-sensitive recurrent ovarian cancer: a meta-analysis using individual patient data. *Ann Oncol*. 2013;24(12):3028–34.
60. Joly F, Ray-Coquard I, Fabbro M, Donoghoe M, Boman K, Sugimoto A, et al. Decreased hypersensitivity reactions with carboplatin-pegylated liposomal doxorubicin compared to carboplatin-paclitaxel combination: analysis from the GCG CALYPSO relapsing ovarian cancer trial. *Gynecol Oncol*. 2011;122(2):226–32. *Analysis of the incidence of HSRs to carboplatin in a large cohort of patients receiving different drug combinations.*
61. Sugimoto H, Iwamoto T, Murashima Y, Tabata T, Sagawa N, Okuda M. Risk factors contributing to the development of carboplatin-related delayed hypersensitivity reactions in Japanese patients with gynecologic cancers. *Cancer Chemother Pharmacol*. 2011;67(2):415–9.
62. Yu DY, Dahl GV, Shames RS, Fisher PG. Weekly dosing of carboplatin increases risk of allergy in children. *J Pediatr Hematol Oncol*. 2001;23(6):349–52.
63. Koren C, Yerushalmi R, Katz A, Malik H, Sulkes A, Fenig E. Hypersensitivity reaction to cisplatin during chemoradiation therapy for gynecologic malignancy. *Am J Clin Oncol*. 2002;25(6):625–6.
64. Li Q, Cohn D, Waller A, Backes F, Copeland L, Fowler J, et al. Outpatient rapid 4-step desensitization for gynecologic oncology patients with mild to low-risk, moderate hypersensitivity reactions to carboplatin/cisplatin. *Gynecol Oncol*. 2014;135(1):90–4.
65. Pawankar R, Canonica GW, Holgate ST, Lockey RF. WAO White Book on Allergy 2011–2012: Executive Summary. World Allergy Organization; Milwaukee, WI, USA. 2011:1–24.
66. Markman M, Zanotti K, Kulp B, Peterson G, Markman M. Relationship between a history of systemic allergic reactions and risk of subsequent carboplatin hypersensitivity. *Gynecol Oncol*. 2003;89(3):514–6.
67. Moon DH, Lee JM, Noonan AM, Annunziata CM, Minasian L, Houston N, et al. Deleterious BRCA1/2 mutation is an independent risk factor for carboplatin hypersensitivity reactions. *Br J Cancer*. 2013;109(4):1072–8.
68. Elligers KT, Davies M, Sanchis D, Ferencz T, Saif MW. Rechallenge with cisplatin in a patient with pancreatic cancer who developed a hypersensitivity reaction to oxaliplatin. Is skin test useful in this setting? *JOP : J Pancreas*. 2008;9(2):197–202.
69. Enrique E, Malek T, Castello JV, de Mateo JA. Usefulness of skin testing with platinum salts to demonstrate lack of cross-reactivity between carboplatin and cisplatin. *Ann Allergy Asthma Immunol*. 2008;100(1):86.
70. Jones R, Ryan M, Friedlander M. Carboplatin hypersensitivity reactions: re-treatment with cisplatin desensitisation. *Gynecol Oncol*. 2003;89(1):112–5.
71. Syrigou E, Makrilia N, Vassias A, Nikolaidis I, Xyla V, Manolopoulos L, et al. Administration of cisplatin in three patients with carboplatin hypersensitivity: is skin testing useful? *Anti-Cancer Drugs*. 2010;21(3):333–8.
72. Dizon DS, Sabbatini PJ, Aghajanian C, Hensley ML, Spriggs DR. Analysis of patients with epithelial ovarian cancer or fallopian tube carcinoma retreated with cisplatin after the development of a carboplatin allergy. *Gynecol Oncol*. 2002;84(3):378–82.
73. Zweig S, Roman LD, Muderis L. Death from anaphylaxis to cisplatin: a case report. *Gynecol Oncol*. 1994;53(1):121–2.
74. Meyer L, Zuberbier T, Worm M, Oettle H, Riess H. Hypersensitivity reactions to oxaliplatin: cross-reactivity to carboplatin and the introduction of a desensitization schedule. *J Clin Oncol*. 2002;20(4):1146–7.
75. Taylor SE, Beck TL, Krivak TC, Zorn KK, Kelley JL, Edwards RP. Oxaliplatin salvage for recurrent ovarian cancer: a single institution's experience in patient populations with platinum resistant disease or a history of platinum hypersensitivity. *Gynecol Oncol*. 2014;134(1):68–72.
76. Rose PG, Metz C, Link N. Desensitization with oxaliplatin in patients intolerant of carboplatin desensitization. *Int J Gynecol Cancer*. 2014;24(9):1603–6.
77. Michikami H, Minaguchi T, Ochi H, Onuki M, Okada S, Matsumoto K, et al. Safety and efficacy of substituting nedaplatin

- after carboplatin hypersensitivity reactions in gynecologic malignancies. *J Obstet Gynaecol Res.* 2013;39(1):330–5.
78. Arimoto T, Oda K, Nakagawa S, Kawana K, Tsukazaki T, Adachi K, et al. Retreatment with nedaplatin in patients with recurrent gynecological cancer after the development of hypersensitivity reaction to carboplatin. *J Obstet gynaecol Res.* 2013;39(1):336–40.
 79. Pichler W. Drug hypersensitivity reactions: classification and relationship to T-cell activation. Pichler, WJ (ed): *Drug Hypersensitivity* Basel, Karger, 2007, pp 168–189.
 80. Markman M, Zanotti K, Peterson G, Kulp B, Webster K, Belinson J. Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. *J Clin Oncol.* 2003;21(24):4611–4. *Large prospective study that evaluates the value of the skin testing to carboplatin in predicting hypersensitivity to carboplatin in subsequent exposures.*
 81. Lee CW, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: standard protocol effective in 57 patients for 255 courses. *Gynecol Oncol.* 2005;99(2):393–9.
 82. Patil SU, Long AA, Ling M, Wilson MT, Hesterberg P, Wong JT, et al. A protocol for risk stratification of patients with carboplatin-induced hypersensitivity reactions. *J Allergy Clin Immunol.* 2012;129(2):443–7. *Highlights the value of repeated skin testing in patients with remote reactions to platinum drugs.*
 83. Pagani M, Venemalm L, Bonnadona P, Vescovi PP, Botelho C, Cernadas JR. An experimental biological test to diagnose hypersensitivity reactions to carboplatin: new horizons for an old problem. *Jpn J Clin Oncol.* 2012;42(4):347–50.
 84. Caiado J, Venemalm L, Pereira-Santos MC, Costa L, Barbosa MP, Castells M. Carboplatin-, oxaliplatin-, and cisplatin-specific IgE: cross-reactivity and value in the diagnosis of carboplatin and oxaliplatin allergy. *J Allergy Clin Immunol Pract.* 2013;1(5):494–500.
 85. Sala-Cunill A, Cardona V, Labrador-Horrillo M, Luengo O, Estes O, Garriga T, et al. Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. *Int Arch Allergy Immunol.* 2013;160(2):192–9.
 86. Cardet JC, Castells MC, Hamilton MJ. Immunology and clinical manifestations of non-clonal mast cell activation syndrome. *Curr Allergy Asthma Rep.* 2013;13(1):10–8.
 87. Douaiher J, Succar J, Lancerotto L, Gurish MF, Orgill DP, Hamilton MJ, et al. Development of mast cells and importance of their tryptase and chymase serine proteases in inflammation and wound healing. *Adv Immunol.* 2014;122:211–52.
 88. Curtis BR, Kaliszewski J, Marques MB, Saif MW, Nabelle L, Blank J, et al. Immune-mediated thrombocytopenia resulting from sensitivity to oxaliplatin. *Am J Hematol.* 2006;81(3):193–8.
 89. Taleghani BM, Meyer O, Fontana S, Ahrens N, Novak U, Borner MM, et al. Oxaliplatin-induced immune pancytopenia. *Transfusion.* 2005;45(5):704–8.
 90. Masse MS, Caimmi D, Demoly P. A delayed reaction to oxaliplatin. *J Investig Allergol Clin Immunol.* 2012;22(5):372–3.
 91. McAlpine JN, Kelly MG, O'Malley DM, Azodi M, Coombe K, Schwartz PE, et al. Atypical presentations of carboplatin hypersensitivity reactions: characterization and management in patients with gynecologic malignancies. *Gynecol Oncol.* 2006;103(1):288–92.
 92. Lee C, Gianos M, Klaustermeyer WB. Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents. *Ann Allergy Asthma Immunol.* 2009;102(3):179–87. *quiz 87-9, 222.*
 93. Caiado J, Picard M. Diagnostic tools for hypersensitivity to platinum drugs and taxanes: skin testing, specific IgE, and mast cell/basophil mediators. *Curr Allergy Asthma Rep.* 2014;14(8):451.
 94. Banerji A, Lax T, Guyer A, Hurwitz S, Camargo Jr CA, Long AA. Management of hypersensitivity reactions to carboplatin and Paclitaxel in an outpatient oncology infusion center: a 5-year review. *J Allergy Clin Immunol Pract.* 2014;2(4):428–33.
 95. National Cancer Institute, Common Terminology Criteria for Adverse Events v4.0. NCI, NIH, DHHS. May 29, 2009. NIH publication # 09-7473.
 96. Brown SG. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol.* 2004;114(2):371–6.
 97. Brandi G, Pantaleo MA, Galli C, Falcone A, Antonuzzo A, Mordenti P, et al. Hypersensitivity reactions related to oxaliplatin (OHP). *Br J Cancer.* 2003;89(3):477–81.
 98. Takase N, Matsumoto K, Onoe T, Kitao A, Tanioka M, Kikukawa Y, et al. 4-step 4-h carboplatin desensitization protocol for patients with gynecological malignancies showing platinum hypersensitivity: a retrospective study. *Int J Clin Oncol.* 2014. doi:10.1007/s10147-014-0731-1.
 99. Sakaeda T, Kadoyama K, Yabuuchi H, Nijima S, Seki K, Shiraishi Y, et al. Platinum agent-induced hypersensitivity reactions: data mining of the public version of the FDA adverse event reporting system, AERS. *Int J Med Sci.* 2011;8(4):332–8.
 100. Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, Guillen-Ponce C, Sanz ML, Alvarez-Cuesta E. Desensitizing oxaliplatin-induced fever: a case report. *J Investig Allergol Clin Immunol.* 2013;23(6):435–6.
 101. Santini D, Tonini G, Salerno A, Vincenzi B, Patti G, Battistoni F, et al. Idiosyncratic reaction after oxaliplatin infusion. *Ann Oncol.* 2001;12(1):132–3.
 102. Ulrich-Pur H, Penz M, Fiebigler WC, Schull B, Kornek GV, Scheithauer W, et al. Oxaliplatin-induced fever and release of IL-6. *Oncology.* 2000;59(3):187–9.
 103. Syrigou E, Syrigos K, Saif MW. Hypersensitivity reactions to oxaliplatin and other antineoplastic agents. *Curr Allergy Asthma Rep.* 2008;8(1):56–62.
 104. Leonard GD, Wright MA, Quinn MG, Fioravanti S, Harold N, Schuler B, et al. Survey of oxaliplatin-associated neurotoxicity using an interview-based questionnaire in patients with metastatic colorectal cancer. *BMC Cancer.* 2005;5:116.
 105. Brockow K, Garvey LH, Aberer W, Atanaskovic-Markovic M, Barbaud A, Biló MB, et al. Skin test concentrations for systemically administered drugs—an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy.* 2013;68(6):702–12.
 106. Martin-Lazaro J, Firvida JL, Berges-Gimeno P. Anaphylaxis after oxaliplatin allergy skin testing. *J Investig Allergol Clin Immunol.* 2014;24(4):269–70.
 107. Iwamoto T, Yuta A, Tabata T, Sugimoto H, Gabazza EC, Hirai H, et al. Evaluation of basophil CD203c as a predictor of carboplatin-related hypersensitivity reaction in patients with gynecologic cancer. *Biol Pharm Bull.* 2012;35(9):1487–95. *Value of BAT as a diagnostic tool for the diagnosis of hypersensitivity to platinum drugs.*