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Platin chemotherapy hypersensitivity reactions: expanding the scope of practice and improving care

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TO THE EDITOR:

Platin-based chemotherapeutic agents are associated with hypersensitivity reactions (HSRs), occurring in 12% of patients with gynecologic malignancy receiving carboplatin.[1] HSRs occur in 5–16% of patients with gynecologic malignancy receiving cisplatin, and up to 25% in patients with multiple cancer types (including gynecologic) receiving oxaliplatin.[2–3] Platin HSRs may lead to use of alternative therapies with potentially worse outcomes particularly for platin responsive-tumors.[4] Although skin testing (ST), desensitization and risk stratification protocols for platin HSRs allow patients to safely receive platins, they are not widely used.[5]

To better understand the safety of platin ST, we conducted a literature review from January 2000 to June 2018 (Table 1) using the following search terms in PubMed: carboplatin ST (69 results), cisplatin ST (95 results), oxaliplatin ST (44 results), and platinum ST (166 results). Other search terms (e.g., carboplatin testing, cisplatin testing, oxaliplatin testing, platin ST) did not yield additional articles. We found 44 studies describing 1,393 patients who received platin ST. Two (0.1%) systemic reactions occurred immediately after ST. One patient with positive carboplatin intradermal testing (concentration not reported) developed symptoms 30 minutes later: diffuse erythroderma and subjective chills, dyspnea, and chest discomfort.[6]

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The authors reported no signs of anaphylaxis. Symptoms resolved with corticosteroids and antihistamines. The patient did not receive further platin agents. The second patient, a 45 year-old woman with metastatic colorectal cancer, developed eyelid swelling, chest erythema, diffuse pruritus, and restlessness 15 minutes after a positive intradermal oxaliplatin test (0.5 mg/mL).[7] The patient received intramuscular epinephrine, intravenous dexclorpheniramine and hydrocortisone. Symptoms resolved within minutes. The patient underwent an oxaliplatin 12-step desensitization with premedication (aspirin, montelukast, ranitidine, and dexchlorpheniramine). At the last step, the patient experienced pruritus on the palms and soles. The infusion was stopped, and the patient received dexchlorpheniramine. The infusion was restarted after 30 minutes at the last step, which the patient tolerated. The patient underwent four additional desensitizations without reaction.

Experience at our own institution supports the safety of platin ST. Our group performed platin ST (Figure 1) on 179 patients from October 2013 to May 2018, and no systemic reactions during ST occurred. Despite this safety profile, there is a theoretical risk of anaphylaxis with any allergy testing procedure. It is important to perform ST in a supervised medical setting with trained staff and emergency and hypersensitivity medications (such as epinephrine, glucagon, corticosteroids, antihistamines, and albuterol) available. Chemotherapy ST is resource-intensive and requires careful planning prior to implementation. Allergy practices need access to a pharmacy that prepares chemotherapy dilutions, and staff trained to handle chemotherapeutic agents safely with appropriate personal protective equipment.

Platin drug challenge, although not routinely performed in the United States, has been studied in platin HSR evaluations.[8,9] In a 2013 study, low-risk patients with platin HSRs and negative platin ST underwent platin challenge; 7 out of 12 (58%) were negative and did not need desensitization.[8] Another study concluded that antineoplastic drug challenges can reduce desensitizations (32% of platin challenges were negative).[9] However, there were 21 positive platin challenges and one patient had anaphylaxis (hives, hypoxemia, hypotension, dyspnea, and wheezing) and required epinephrine. Platin drug challenges may be harder to spread in the United States because of this high risk of HSR.

Risk stratification and drug desensitization are critical steps in HSR evaluation. Our group developed and published chemotherapy risk stratification algorithms that identify patients that are not allergic (see Figure E1 in the Online Repository). Patients start in the inpatient setting, generally with an intermediate desensitization protocol (see Figure E2 in the Online Repository).[5] Protocol progression is determined by undergoing desensitization without reactions and remaining negative on repeat ST. The risk stratification process identifies patients who are not allergic to platin agents, despite a supposed allergic reaction history. The goal is for non-allergic patients to safely return to outpatient treatments, typically at a 50% infusion rate. By reducing the number of inpatient desensitizations, this progression ideally leads to increased patient satisfaction and compliance, as well as cost savings, while ensuring the safety of these patients.

While chemotherapy desensitization is safe and effective, it is also resource-intensive.[5]

Desensitizations require prolonged infusions, dedicated infusion beds/chairs, pharmacy access to chemotherapy, trained staff, and space, which increase costs. At our institution, we implemented an outpatient infusion chair program in which patients at low risk for HSR (e.g. no or minimal reactions during prior desensitizations) receive their desensitization in an outpatient infusion chair. These desensitizations are treated as outpatient procedures. Chemotherapy orders and dilutions are prepared in advance to ensure a timely start. In a process improvement analysis, we showed that utilizing outpatient chemotherapy desensitization chairs shortened time to starting desensitizations and increased patient satisfaction, while maintaining safety.[10] This work suggests that low-risk desensitizations appear safe to conduct in an outpatient setting.

Despite the utility and safety of chemotherapy ST and desensitization, these procedures are infrequently performed. In early 2018, we conducted a national survey of practicing allergy/immunology physicians, via an email through the AAAAI leadership. Our 8-question survey aimed to investigate practice patterns for chemotherapy HSR evaluation. Though few respondents (13/72; 18%) performed chemotherapy ST in their office or performed desensitizations, most respondents (51/71; 72%) expressed interest in learning how to implement these protocols (unpublished data). The major limitation of this survey study was the low response rate (9% of AAAAI membership, consistent with average AAAAI survey response rates). Still, these survey results highlighted respondents' interest in education about chemotherapy testing.

In summary, chemotherapy ST, risk stratification, and desensitization can be performed safely and improve patient outcomes. A platin HSR should not lead to use of second-line agents, as allergic patients can safely receive chemotherapy through desensitization. Risk stratification protocols can identify non-allergic patients, allowing first-line therapy and returning patients to an outpatient setting for infusions.[5] Though many practices may not have every resource needed for desensitization, they can begin the process with ST and/or risk stratification. Those patients that require desensitization can then be referred to desensitization centers. Allergists can safely expand their scope of practice and work closely with oncologists to improve patient care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. 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;17:1141. [PubMed: 10561172]
2. 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;25:625–626. [PubMed: 12478013]

3. 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;76:36–41. [PubMed: 19033714]
4. Bruchim I, Jarchowsky-Dolberg O, Fishman A. Advanced (>second) line chemotherapy in the treatment of patients with recurrent epithelial ovarian cancer. Eur J Obstet Gynecol Reprod Biol. 2013;166:94–98. [PubMed: 23088893]
5. Wang AL, Patil SU, Long AA, Banerji A. Risk-stratification protocol for carboplatin and oxaliplatin hypersensitivity: repeat skin testing to identify drug allergy. Ann Allergy Asthma Immunol. 2015;115:422–428. [PubMed: 26298407]
6. 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;21:4611–4614. [PubMed: 14673050]
7. Martin-Lazaro J, Firvida JL, Berges-Gimeno P. Anaphylaxis after oxaliplatin allergy skin testing. J Investig Allergol Clin Immunol. 2014;24:269–270.
8. Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, Ferreiro-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;68:853–861. [PubMed: 23647576]
9. Alvarez-Cuesta E, Madrigal-Burgaleta R, Angel-Pereira D, Ureña-Tavera A, Zamora-Verduga M, Lopez-Gonzalez P, et al. Delving into cornerstones of hypersensitivity to antineoplastic and biological agents: value of diagnostic tools prior to desensitization. Allergy. 2015;70:784–794. [PubMed: 25832325]
10. Barmettler S, Wolfson A, Slawski B, Jordan J, Blumenthal K, Banerji A. Safe and effective implementation of chemotherapy outpatient desensitizations [abstract]. Ann Allergy Asthma Immunol. 2017;119:S2.

Clinical Implications:

- Hypersensitivity reactions to platin chemotherapy are common and associated with worse patient outcomes when first-line treatment is consequently avoided. Platin chemotherapy skin testing and desensitization are safe, improve patient care, and should be utilized more broadly by allergists.

MASSACHUSETTS GENERAL HOSPITAL

MGH ALLERGY ASSOCIATES

Chemotherapy Skin Testing (#1)

Carboplatin (Paraplatin), Cisplatin (Platinol), Oxaliplatin (Eloxatin)

Date:_____

Chemo Expiration Date:

Carboplatin:_____Cisplatin:_____

Oxaliplatin:_____

Patient name

MGH #

DOB

Directions:

1. Place tests on arms.
2. For intradermal testing, inject 0.02ml of testing drug at each site.
3. Measure test sites 15 minutes after placement
4. Record largest diameter *wheal X flare* at test site in millimeters.
5. Test is positive if test site reveals a wheal and flare within 15 minutes of placement. **Stop** testing reactive drug immediately.

		Carboplatin	Cisplatin	Oxaliplatin	Normal Saline	Histamine
Step 1	**Epicutaneous** (Greer pick)	10 mg/ml	1 mg/ml	5 mg/ml		(6 mg/ml)
Step 2	**Intradermal**	0.1 mg/ml	0.01 mg/ml	0.05 mg/ml		(0.1 mg/ml)
Step 3	**Intradermal**	1 mg/ml	0.1 mg/ml	0.5 mg/ml		
Step 4	**Intradermal**	5 mg/ml	1 mg/ml	5 mg/ml		

Comments:_____

_____

Tester's signature:_____

FIGURE 1.
Platin ST Protocol

TABLE 1.

Published studies with platin skin testing since 2000

Author (last name)	Year	Drug(s) tested: Ca, Cis, O	Total number of patients	Systemic reactions
Zanotti	2001	Ca	47	None
Meyer	2002	O	8	Not discussed
Porzio	2002	Ca, Cis	1	None
Garufi	2003	O	5	Not discussed
Markman	2003	Ca	126	"A single individual developed a 3-cm wheal and flare around the injection site that progressed over a few minutes to total body erythroderma. The patient complained of chills, chest discomfort, and mild dyspnea, but there were no other signs of severe anaphylaxis (e.g., wheezing, intense anxiety, hypotension). After treatment with diphenhydramine and corticosteroids, the symptoms completely resolved."
Moreno-Ancillo	2003	Ca	1	Not discussed
Thomas	2003	O	3	Not discussed
Choi	2004	Ca	8	Not discussed
Lee	2004	Ca	5	Not discussed
Confino-Cohen	2005	Ca	23	Not discussed
Lee	2005	Ca	26	Not discussed
Herrero	2006	O	5	Not discussed
McAlpine	2006	Ca	12	None
Edmondson	2007	O	1	None
Leguy-Seguin	2007	Ca, Cis, O	21	None
Castells	2008	Ca	88	Not discussed
Enrique	2008	Ca	2	Not discussed
Pagani	2008	O	4	None
Gomez	2009	Ca	54	Not discussed
Hesterberg	2009	Ca	38	Not discussed
Syrigou	2009	Ca	3	None
Visitsunthorn	2009	Ca	2	None
Gottlieb	2010	Ca, O	11	None
Herrera	2010	Ca	1	None
Gastaminza	2011	Ca, O	2	None
Pagani	2012	Ca	3	Not discussed
Patil	2012	Ca	39	Not discussed
Caiado	2013	Ca, O	12	Not discussed
Cortijo-Cascajares	2013	O	21	Not discussed
Madrigal-Burgaleta	2013	Ca, Cis, O	32	Not discussed
Wong	2013	O	46	Not discussed
Bruchim	2014	Ca	49	None

Author (last name)	Year	Drug(s) tested: Ca, Cis, O	Total number of patients	Systemic reactions
Martin-Lazaro	2014	O	1	"Within 15 minutes, the patient began to experience itching of the eyes and nose, palpebral swelling, generalized pruritus (especially on the palms, soles and genitals), chest erythema, and restlessness. She received intramuscular epinephrine, and intravenous dexchlorpheniramine and hydrocortisone, and recovered within minutes. She did not experience any delayed reaction."
Alvarez-Cuesta	2015	Ca, Cis, O	74	Not discussed
D'Amelio	2015	Ca, Cis, O	1	None
Wang	2015	Ca, O	142	Not discussed
Altwerger	2017	Ca	129	Not discussed
Brault	2017	Ca, Cis, O	86	Not discussed
Galvao	2017	Ca	138	Not discussed
Giavina-Bianchi	2017	Ca, O	15	Not discussed
Mawhirt	2017	Ca, O	36	Not discussed
Solomon	2017	Cis	1	None
Capelle	2018	Ca, Cis	22	Not discussed
Perez-Rodriguez	2018	Ca, Cis, O	49	Not discussed

Ca, carboplatin; *Cis*, cisplatin; *O*, oxaliplatin.