

Novel Roles for Platinum and Taxane Agent Skin Testing in Risk Stratification of Chemotherapy Hypersensitivity



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In this issue of *the Journal of Allergy and Clinical Immunology: in Practice*, Pradelli et al¹ report their 6-year experience evaluating and managing hypersensitivity reactions (HSRs) to platinum and taxane agents. Their findings raise interesting questions regarding the roles of skin testing (ST) and desensitization protocols in platinum and taxane HSR evaluation and management. Desensitization protocols in the treatment of cancer patients with hypersensitivity to their first-line therapy have gained momentum in the last 10 years and created critical collaborations between allergists and oncologists.² A central role has emerged for the allergist in evaluating the mechanisms of these reactions, providing risk stratification, and designing personalized protocols, which have had a dramatic impact on the patient's quality of life and life span. Safety and efficacy are hallmarks of desensitization protocols and the role of ST and its negative predictive value leading to challenges versus desensitization is explored in this article.

ST has a relatively well-established role in determining which desensitization protocol can be used safely after suspected HSRs to platinum agents.³ The value of ST in predicting whether a patient can tolerate reintroduction without desensitization of the same agent is less clear. One study of 64 patients found the positive predictive value of oxaliplatin ST to be 92% (95% CI, 81.4-102.6), with 2 oxaliplatin ST-positive patients subsequently tolerating reintroduction without desensitization. However, the negative predictive value of oxaliplatin ST was low at 56.4% (95% CI, 40.8-72.0).⁴ Other reports have varied, with 4 carboplatin ST-negative patients experiencing mild HSRs with carboplatin reintroduction without desensitization,⁵ 6 carboplatin ST-negative patients tolerating carboplatin reintroduction without desensitization,⁶ and 10 oxaliplatin ST-negative patients tolerating oxaliplatin reintroduction without desensitization.⁶

The authors report that 50 platinum ST-negative patients subsequently received the same (n = 25) or alternate (n = 25)

platinum agent via graded challenge. Zero reactions occurred in 17 patients who received cisplatin via graded challenge, 2 reactions occurred in 15 patients who received carboplatin via graded challenge, and 2 reactions occurred in 18 patients who received oxaliplatin via graded challenge. It is not reported whether the reactions occurred in patients receiving the same or alternate agent. The graded challenge was performed by administering 3 serial dilutions (1:1000, 1:100, 1:10) over 15-minute intervals each and the remaining dose as a standard 1:1 infusion. Patients who tolerated the graded challenge subsequently received and tolerated platinum agents via standard infusion.

Interestingly, this graded challenge protocol is similar to 4-step desensitization protocols used at other institutions, presented in Table 1.⁷⁻⁹ These 4-step protocols have allowed successful reintroduction with no or tolerable breakthrough HSR for 19 of 20 patients with Common Terminology Criteria for Adverse Events (CTCAE) 4.0 grade I to III HSR,⁷ 59 of 73 patients with carboplatin ST-positive results on routine screening after the sixth carboplatin cycle,⁸ 47 of 56 patients with CTCAE 4.0 grade I to IV HSR,⁸ and 17 of 18 patients with mild/low-moderate (per modified clinical classification system used at that institution) carboplatin HSR.⁹ Pradelli et al's findings suggest that incorporating ST into these existing management strategies has the potential to more accurately identify patients who could tolerate a 4-step reintroduction protocol.

It is important to note that management protocols using ST have shown that gradual tolerance can be induced in most ST-negative patients who receive repeat desensitization.³ Therefore, tolerance of a standard infusion after a 4-step reintroduction protocol suggests but does not necessarily indicate true absence of sensitization. It is still significant that the authors demonstrated a management strategy allowing most ST-negative patients to safely advance to standard infusion, as previous publications advanced ST-negative patients to 50% of the standard infusion rate.³

Timing affects interpretation of platinum ST results, and it is recommended that ST be performed at least 4 to 6 weeks after the initial HSR and repeated serially if the ST is performed more than 6 months after the initial HSR.³ Similarly, the authors found that 5 ST-negative patients who received initial ST during the first 10 days after the initial HSR subsequently reacted on reintroduction of platinum agent and converted to ST-positive. Interestingly, the authors report a window of 2 weeks to be sufficient at preventing initial false-negative ST results, which may be of importance as patients who have experienced platinum HSRs are often referred for time-sensitive evaluation that would benefit from earlier ST.

The authors also provide data that further support previously published observations regarding platinum agent cross-reactivity.

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TABLE I. Four-step reintroduction protocols reported for carboplatin^{1,7-9}

Step	Pradelli et al ¹	Takase et al ⁷	Altwerger et al ⁸	Li et al ⁹
1	1:1000	1:1000	1:1000	1:1
	NR	4.2 mL/min	1.0 mL/min	0.8 mL/min
	15 min	60 min	30 min	15 min
2	1:100	1:100	1:100	1:1
	NR	4.2 mL/min	1.7 mL/min	2.5 mL/min
	15 min	60 min	30 min	15 min
3	1:10	1:10	1:10	1:1
	NR	4.2 mL/min	1.7 mL/min	5.0 mL/min
	15 min	60 min	60 min	15 min
4	1:1	1:1	1:1	1:1
	Standard rate	4.2 mL/min	2.8 mL/min or slower	12.4 mL/min
		60 min	90+ min	45 min

NR, Not reported.

Dilutions, rates, and duration of infusion are reported for each of the 4 steps.

Carboplatin and cisplatin cross-reactivity is thought to be low. Carboplatin-reactive patients have been found to tolerate cisplatin in multiple reports (combined, 42 of 51 carboplatin-reactive patients tolerated cisplatin). Concerningly, 2 of the cases where cisplatin was not tolerated resulted in cisplatin-induced HSR fatalities.³ Indeed, the authors found that 4% of carboplatin-reactive carboplatin ST-positive patients also reacted to cisplatin, in line with a previous publication that found that 7% (3 of 43) of carboplatin-reactive carboplatin ST-positive patients also reacted to cisplatin (Table II).^{1,6} Of note, at least in the Pasteur et al⁶ study, the 3 carboplatin ST-positive patients with positive ST result to cisplatin had previously been exposed to cisplatin. ST could potentially be used to identify select cases of cisplatin cross-reactivity in carboplatin-reactive patients. Pasteur et al⁶ reported in their study that all 15 carboplatin-reactive carboplatin ST-positive cisplatin ST-negative patients were able to tolerate cisplatin via standard infusion. Carboplatin ST reactivity has not been observed in cisplatin-reactive cisplatin ST-positive patients (Table II).^{1,6}

Carboplatin and oxaliplatin cross-reactivity likely exists to some degree. Carboplatin-reactive carboplatin ST-positive patients have been observed to exhibit ST positivity to oxaliplatin, and oxaliplatin-reactive oxaliplatin ST-positive patients also have been observed to have high ST-positive rates to cisplatin (Table II).^{1,6} It is possible that ST could help identify the patient sensitized to carboplatin or oxaliplatin who could tolerate the other platinum agent (eg, a carboplatin-reactive carboplatin ST-positive patient with negative oxaliplatin ST result may have a higher likelihood of tolerating oxaliplatin than one with positive oxaliplatin ST result). However, clinical data regarding tolerance after negative ST result in this situation are limited and more extensive studies are needed.^{1,3,6}

There appears to be an absence of cross-reactivity between cisplatin and oxaliplatin (Table II).^{1,6} One study also reported that 10 oxaliplatin-reactive oxaliplatin ST-positive patients were able to tolerate cisplatin via standard infusion, suggesting that the ST findings reflect clinical tolerability.⁶

ST has a less-established role in the evaluation of taxane reactions, because taxane reactions are thought to be non-IgE-mediated.¹⁰ False-positive ST results occur, with 1 study reporting 4 paclitaxel ST-positive patients subsequently tolerating initial reintroduction via standard infusion.⁴ Risk stratification

TABLE II. Platinum agent ST cross-reactivity^{1,6}

Cross-reactivity with	Carboplatin	Cisplatin	Oxaliplatin
Carboplatin			
Pradelli et al ¹	NA	0% (0 of 4)	18% (6 of 34)
Pasteur et al ⁶		0% (0 of 3)	45% (23 of 51)
Cisplatin			
Pradelli et al ¹	4% (1 of 23)	NA	0% (0 of 34)
Pasteur et al ⁶	7% (3 of 43)		0% (0 of 51)
Oxaliplatin			
Pradelli et al ¹	48% (11 of 23)	0% (0 of 4)	NA
Pasteur et al ⁶	37% (16 of 43)	0% (0 of 3)	

NA, Not applicable/available.

ST results for carboplatin, cisplatin, and oxaliplatin from 2 publications are presented.

based on the initial HSR grade has shown that patients with initial HSR CTCAE grade I can safely receive paclitaxel without ST or desensitization.¹⁰ ST could improve risk stratification for patients with initial HSR CTCAE grade II to IV. A large study (n = 145) showed that 21 of 36 ST-negative patients advanced to standard infusion compared with 13 of 110 ST-positive patients.¹¹ These authors' findings that 14 patients with initial taxane HSR grade I to III and taxane-negative ST received the same (n = 12) or alternate (n = 2) taxane agents via their graded challenge protocol, and that 13 of these patients (1 patient died) subsequently received taxane agents via standard infusion support the use of ST in risk stratification management strategies.

In conclusion, this article provides advanced risk stratification strategies by performing ST in addition to grading the severity of the initial reaction to determine the safety of reintroduction using a 4-step protocol. The authors' findings suggest that negative ST result can identify patients who could be advanced through risk stratification protocols to receive platinum or taxane agents via standard infusion. The authors add to emerging literature regarding platinum agent cross-reactivity, strengthening the evidence that a subset of patients sensitized to one platinum agent may be able to tolerate an alternative without desensitization. As more institutions report on their experience evaluating and managing platinum and taxane agent HSRs, continued improvements can be made to refine existing risk stratification strategies for patients with platinum and taxane HSRs.

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