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Skin testing and desensitization outcomes among platinum-sensitive oncology patients



Platinum-based, immediate hypersensitivity reactions (HSRs) are relatively common, with incidences ranging from 6.5% to 44% for carboplatin and from 10% to 19% for oxaliplatin.¹ Platinum hypersensitivity potentially leads to patient anxiety, delayed chemotherapy administration, or switches to less-preferred regimens. Platinum skin tests (STs) confirm immediate-type reactions in upward of 66%–98% of patients.^{2–5} False-negative results may occur if ST is performed shortly after a platinum-based HSR.⁴ Although breakthrough reactions occur during desensitization, success rates range from 71% to 99% for carboplatin and from 80% to 100% for oxaliplatin.^{1–3,5,6}

We conducted an institutional review board–approved, retrospective review of adult patients (≥18 years old) with a recent history (≤3 months) of platinum immediate-type HSRs. These patients were evaluated by allergist-immunologists at our institution from 2009 to 2016 and identified through a query of Current Procedural Terminology and *International Classification of Disease*—9th/10th revision codes. Patients with physician-documented initial reactions consistent with immediate-type HSRs who received subsequent cycles utilizing desensitization were included in the analysis. Patients' demographics and clinical characteristics reviewed included age, sex, cancer type, self-reported atopic disease history, and/or reported drug allergy. Index platinum HSR details were recorded, including cycle number, symptoms/signs observed, treatments received, and reaction severity.

Skin prick (SP) and/or intradermal (ID) platinum ST results were reviewed. Skin testing was performed (as previously described²), with either carboplatin (Teva Pharmaceuticals USA, Fairfield, New Jersey) or oxaliplatin (Winthrop US-Sanofi SA, Bridgewater, New Jersey), depending on the history, along with histamine-positive and saline-negative controls. If SP testing was positive (wheal >3 mm

compared with the negative control), ID testing was not performed. A single-repeat ST (SP with or without ID) was performed in a subset of patients who had initial negative results. Each practitioner determined the number of desensitization steps based on clinical history, modifying the standard 12-step desensitization protocol² if considered clinically appropriate. All patients received premedication with a combination of systemic corticosteroid, antihistamine, leukotriene-receptor antagonist, and/or aspirin. In cases of desensitization reactions, the severity grade, treatments administered, and infusion status (discontinued or restarted/completed) were reviewed. The platinum index reaction and subsequent desensitization reaction severities were classified using the Brown classification.⁷

Patients' clinical characteristics and history details were summarized using descriptive statistics with mean, median, and frequency. ST results and desensitization outcomes were summarized by identifying frequency. Data were compared using Fisher's exact test, independent two-sample *t* test, Wilcoxon rank sum test, Pearson χ^2 test, and Cochran-Armitage trend test, with exact *P* values computed. Desensitization outcomes were analyzed using a generalized estimating equation to account for the repeated data measurements. *P* ≤ .05 were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Thirty-six patients (age, 63.6 ± 10.1 years; 89% women; carboplatin, *n* = 34; oxaliplatin, *n* = 2) who underwent a total of 146 desensitizations (carboplatin, *n* = 137; oxaliplatin, *n* = 9) were identified. The patients were predominantly Caucasian (83%) and afflicted with gynecologic malignancies (89%). Most index reactions were grade 1 or 2 severity (72%), occurring around the eighth cycle (median, 8; interquartile range [IQR], 6.5–9.5). Patients who tolerated all of their desensitization infusions were classified as desensitization-tolerant, whereas those with at least 1 reaction were

Table 1
Demographics and Clinical Characteristics of Desensitization-Reactive and Desensitization-Tolerant Patients

	Desensitization -reactive	Desensitization -tolerant	All patients	P value
Patients, n	21	15	36	
Age (years) ^a	65.1 ± 8.7	61.5 ± 11.8	63.6 ± 10.1	.30
Women, n (%)	19 (90%)	13 (87%)	32 (89%)	.99
Caucasian, n (%)	20 (95%)	10 (67%)	30 (83%)	.06
Self-reported atopic history, n (%)	3 (14%)	7 (47%)	10 (28%)	.06
Additional reported drug allergies (n) ^b	1 (0–2)	0 (0–1)	0 (0–2)	.18
Cancer type, n (%)				.75
Gynecologic	19 (90%)	13 (87%)	32 (89%)	
Bronchial/pulmonary	1 (4.8%)	0 (0%)	1 (2.8%)	
Gastrointestinal	1 (4.8%)	2 (13%)	3 (8.3%)	
Cycle number of index reaction (n) ^b	8 (5–9)	8 (7–10)	8 (6.5–9.5)	.26
Index reaction severity grade, n (%)				.03
Grade 1	11 (52%)	2 (13%)	13 (36%)	
Grade 2	6 (29%)	7 (47%)	13 (36%)	
Grade 3	4 (19%)	5 (33%)	9 (25%)	
Grade 4	0 (0%)	1 (6.7%)	1 (2.8%)	
Number of desensitizations (n) ^b	4 (2–6)	4 (2–5)	4 (2–5)	.47
Index reaction to initial ST (days) ^b	22 (14–30)	14 (14–30)	14 (14–30)	.78
Initial ST result, n (%)				.88
Positive	9 (43%)	8 (53%)	17 (47%)	
Negative	10 (48%)	6 (40%)	16 (44%)	
Equivocal	2 (9.5%)	1 (6.7%)	3 (8.3%)	

Abbreviation: ST, skin test.

^aData reported as mean (standard deviation).

^bData reported as median (interquartile range).

termed desensitization-reactive. Initial ST (SP with or without ID) was performed in all patients (median, 14 days; IQR, 14–30 days) after the index reaction. The initial ST results were: 9 positive, 10 negative, and 2 equivocal for desensitization-reactive patients (n = 21); and 8 positive, 6 negative, and 1 equivocal for desensitization-tolerant patients (n = 15). Nine patients with initial ST-negative results underwent repeat ST at 1–26 months after their index reactions. The conversion rate to positive was 67% (n = 6 of 9) and included all patients with grade 3 or 4 index reactions. Overall, 86% (n = 24 of 28) of the patients demonstrated a positive ST result, either on initial or repeat testing. There were no differences in initial (P = .88) or repeat ST results (P = .87) between the desensitization-reactive and desensitization-tolerant patient groups. Table 1 summarizes the patients' characteristics.

Each patient underwent a range of 1–12 desensitizations. Ninety-nine desensitizations utilized a 12-step protocol with a starting dilution of 1:100, as described in a previous study.² The overall desensitization completion rate was 97%. Of 146 desensitizations performed, 96 (66%) were completed without reactions, 31 (21%) with cutaneous-only limited reactions, and 19 (13%) with systemic reactions, including anaphylaxis. The 50 total desensitization reactions comprised 31 grade 1 (62%), 16 grade 2 (32%), and 3 grade 3 (6%) anaphylactic reactions requiring epinephrine administration. All desensitization reactions were carboplatin-associated and most occurred during the first 4 desensitizations. For 12-step desensitization reactions (n = 31 of 99), 14 reactions (45%) occurred during steps 8–11 and 17 (55%) occurred during step 12.

There were no differences in clinical characteristics between desensitization-reactive and desensitization-tolerant patients, except that the desensitization-tolerant group comprised a greater proportion of patients with grade 3 or 4 index reaction severity (P = .03), confirmed using the Cochrane-Armitage trend test. The desensitization reaction rates were as follows: 30% ST initial-positive patients; 34% ST converters; and 35% ST-negative patients. Although we lacked sufficient analysis power, 67% of ST converters mostly had grade 3 or 4 index reactions compared with 18% of ST initial-positive and none of the ST-negative patients. Among desensitization reactions, 40% were grade 2 and 10% were grade 3 for

ST converters vs 22% (grade 2 only) for ST initial-positive and 33% (grade 2 only) for ST-negative patients.

In conclusion, we have presented ST results and desensitization outcomes in patients after recent platinum HSRs. Platinum hypersensitivity was confirmed in most patients (86%) via positive initial or repeat ST. Neither clinical characteristics nor ST results predicted desensitization outcomes in our patient population. Due to the possibility of anergic ST results, as most testing was performed within 4 weeks of an initial HSR,⁴ desensitization protocols were utilized in all patients with immediate-type HSR history. It is our opinion that a negative or equivocal ST result should not alter the decision for desensitization if the patient's history is suggestive of immediate-type hypersensitivity to the platinum chemotherapeutic agent in question. Our study also suggests that ST converters with recent HSRs present with more severe index reactions and may be at risk for more severe desensitization reactions with repeated platinum exposures.

Our high desensitization completion rate of 97% is consistent with findings from earlier studies.^{2,3,6} Moreover, most desensitizations resulted in mild or no reactions and were less severe compared with the index HSR severity in patients.^{2,5,6} Although our study was limited by its retrospective design at a single center and had a relatively small sample size, it demonstrates that 12-step and modified desensitizations performed at a university-affiliated, community-based institution are effective in reducing reaction severity or preventing reactions from the outset. Our data affirm that the vast majority of patients with platinum hypersensitivity can successfully receive additional cycles utilizing desensitization.

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Is there a link between nasal polyposis and increased risk for sinonasal malignancy?



Sinonasal polyposis is a condition that can be present in both allergic and nonallergic clinical settings. The specific relationship between sinonasal polyps and sinonasal malignancies has not been well described. With regard to allergic etiologies, there is some suggestion that those individuals with atopy in general may be at higher risk of lymphoma.^{1,2} One population-based study demonstrated an association with allergic rhinitis and nasopharyngeal carcinoma.³ Another study evaluated 22 patients with newly diagnosed nasopharyngeal carcinoma, 4.5% of whom had allergic rhinitis.⁴ There have been isolated case reports describing the presence of nasal polyps and nasopharyngeal carcinoma.^{5,6} In surveillance evaluation of patients after radiotherapy for nasopharyngeal carcinoma, 1% (n = 11) of patients were found to have nonmalignant polyps and masses of the nasopharynx,⁷ 10 of whom had a history of chronic nasopharyngitis before the diagnosis of nasopharyngeal carcinoma. Although there have been case reports describing the difficulty distinguishing nasal polyps from malignancy in the nasopharynx, due to similar gross features on nasal endoscopy,^{8–10} an extensive literature review did not reveal any study correlating nasal polyposis and its association with sinonasal malignancies. The purpose of this study was to assess the incidence of patients with existing nasal polyposis who subsequently develop new sinonasal malignancies, including lymphoma, squamous cell carcinoma, nasopharyngeal carcinoma, inverted papilloma, and mucosal melanoma.

This study was approved by the institutional review board of Kaiser Permanente Southern California (KPSC). Patients with pre-existing nasal polyposis (exposed) in the January 2004 to December 2013 study period were matched with patients without nasal polyposis (unexposed). To be eligible for the matched cohort, exposed subjects had to have at least 1 year of continuous health plan membership (45-day gap allowed) before diagnosis with nasal polyps, and unexposed subjects had to have at least 2 years of continuous membership at any point in the study period. Eligible exposed subjects were then matched with at least 1 and up to 5 eligible unexposed subjects on the basis of age $\pm$ 1 year, same sex, same race/ethnicity, and similar time of membership at KPSC. No unexposed subject could be matched more than once and matched unexposed subjects received the same index date of their respective exposed subjects, which was the date of diagnosis with nasal polyposis. All subjects with a previous malignancy before the index date were excluded.

Sociodemographic characteristics were electronically captured from the electronic health record for all subjects relative to the index date. These included age, sex, race/ethnicity, history of tobacco or alcohol use, and Quan's adaptation of the Charlson Comorbidity Index, a commonly used index of comorbidity that is highly predictive of 10-year risk of death. Tobacco and alcohol use are routinely screened at the office visit through patient-provider dialogue. Incident and prevalent malignancies were captured using KPSC's Surveillance, Epidemiology and End Results affiliated cancer registry. Length of follow-up, in years, was estimated for all subjects from the index date through the earliest of either December 31, 2014, disenrollment from the health plan, death, or incident cancer diagnosis.

The study outcomes of interest included the development of specific head and neck malignancies and all-cause mortality. The head and neck region included malignancy involving the eye, floor of mouth, gum, hypopharynx, larynx, lip, nasal cavity, sinus, ear, nasopharynx, salivary gland, tongue, tonsil, oropharynx, and other sites in the lip oral cavity and pharynx.

Assessment of potential confounders was made for all measured patient characteristics at baseline. Examination of the association between nasal polyp exposure status and each study outcome was made using crude and multivariable adjusted Cox proportional hazards models, which adjusted for the confounding effects of statistically significant sociodemographic factors identified in the previous step. All hypothesis tests were two-sided and considered significant at the 5% type I error rate. All analyses were conducted using SAS Enterprise Guide version 5.1 (SAS Institute, Inc, Cary, North Carolina).

There were more than 14 million members active at any point between January 1, 2004 and December 31, 2013 at KPSC, of whom 21,026 were diagnosed with nasal polyps (exposed). We identified 4,533,291 eligible members without a diagnosis of nasal polyps (unexposed) and matched 16,791 exposed members to 82,801 unexposed members. After exclusion of previous malignancy, our final cohort consisted of 95,066 members, of whom 15,852 had nasal polyps.

On average, patients were followed for 4.9 (standard deviation, 3.0) years and, of the head or neck malignancies, squamous cell carcinoma and lymphoma had the highest incidence, with 91 (0.1%) and 149 (0.2%), respectively, occurring in the overall study population. All-cause mortality occurred in 4,750 of the unexposed and 765 of the exposed members.

Finally, our examination of the risk associations between nasal polyp exposure status and the study outcomes is detailed in Table 1.