




Safety and efficacy of an outpatient 12-step desensitization protocol for antineoplastic agents

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HIGHLIGHTS

- ⇒ Hypersensitivity reactions may preclude further treatment with the antineoplastic agent.
- ⇒ Our outpatient 12-step desensitization protocol incorporates premedication and extended infusion.
- ⇒ The protocol led to successful desensitization to antineoplastic agents, without associated death.

ABSTRACT

Objective Antineoplastic agents can cause hypersensitivity reactions that may preclude further treatment, possibly compromising patient outcome if the tumor remains sensitive to such agent. Although desensitization protocols can be used to re-introduce agents after the development of a hypersensitivity reaction, these protocols vary across institutions. Our study evaluated the safety and efficacy of our desensitization protocol.

Methods All patients who underwent desensitization to platinum, taxane, liposomal doxorubicin, or trastuzumab between November 2016 and May 2021 after a prior hypersensitivity reaction to the specific agent were included in a retrospective review. The 12-step, outpatient desensitization protocol included pretreatment with a leukotriene receptor antagonist, antihistamines, and corticosteroids, as well as extended infusion times. Successful desensitization was defined as the completion of ≥ 3 cycles without discontinuation of the agent due to a hypersensitivity reaction.

Results A total of 186 eligible patients were included. Median age was 59.5 years (range 26–87). 155 (83%) patients were treated with platinum. 55 (30%) patients were treated for colorectal cancer and 52 (28%) for ovarian cancer. 104 (56%) patients completed ≥ 3 cycles of therapy during desensitization. The median infusion time was 380 min (range 325–360 min). The median number of desensitization cycles was 3, with 694 cycles completed among all patients. A total of 79 (42%) patients had a breakthrough hypersensitivity reaction during desensitization, 4 of whom required epinephrine, and 84 (45%) patients discontinued the agent undergoing desensitization due to progression of disease.

Conclusions Our outpatient 12-step, institutional desensitization protocol for antineoplastic therapy proved safe and efficacious, with 56% of patients successfully completing ≥ 3 cycles and not requiring an inpatient admission.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Desensitization protocols involve premedication and the administration of incrementally increasing doses of the agent as an extended infusion in order to safely re-introduce the drug following a hypersensitivity reaction.

WHAT THIS STUDY ADDS

- ⇒ This study describes a single-institution outpatient 12-step desensitization protocol for antineoplastic agents. The desensitization protocol was shown to be safe and facilitated successful desensitization to antineoplastic agents following a hypersensitivity reaction.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This outpatient protocol can be used as a template for the development of desensitization protocols at other institutions. Future studies confirming survival benefits of such desensitization protocols are needed.

INTRODUCTION

Hypersensitivity reactions can occur after initial or repeated exposure to an anticancer agent, typically necessitating discontinuation of the agent, as severe reactions can be fatal.¹ Antineoplastic agents most frequently associated with hypersensitivity reactions include platinum agents, taxanes, anthracyclines, and monoclonal antibodies,^{2,3} which are often the most effective agents for many solid tumors, including gastrointestinal and gynecological cancers. Discontinuation of a therapy after a hypersensitivity reaction may negatively impact outcomes in patients still responding to the agent. Transition to an alternative agent may be considered, and has been shown to be effective in some studies.⁴ However, response rates may vary, and there is potential for cross-reactivity

among medications of the same class, which may preclude further treatment with an agent from that class.^{4–7} Furthermore, the unique toxicity profile of each agent may further limit drug substitution. For instance, cisplatin would not be a suitable alternative for carboplatin in a patient with pre-existing neuropathy and/or renal impairment.⁸ Similarly, docetaxel compared with paclitaxel is associated with a higher risk of neutropenia but lesser risk of neurotoxicity.⁹

The incidence of hypersensitivity reactions due to platinum agents, including oxaliplatin, cisplatin, and carboplatin, is 4.6–25%.¹⁰ The most important risk factor for hypersensitivity reaction development to a platinum agent is previous platinum exposure, with reactions often occurring during the seventh to ninth infusion.¹⁰ Compared with platinum-associated hypersensitivity reactions, which tend to be acquired, taxane-associated hypersensitivity reactions occur in up to 10% of patients, usually at initial exposure despite premedication with corticosteroids and antihistamines.¹¹ The solvents used to stabilize taxanes, including cremophor and polysorbate, and the hydrophilic coating of liposomal drugs with polyethylene glycols, can lead to complement activation and are usually the cause of reactions associated with these agents.^{12–13} Hypersensitivity reactions to monoclonal antibodies are typically related to cytokine release in response to structural components of the antibody.¹⁴

Current recommendations include discontinuation of the antineoplastic agent after the development of severe reactions.¹⁵ Transition to an alternative agent within the same class is associated with improved survival compared with treatment discontinuation or changing to an agent from another class; however, some patients may derive the most benefit from continuation of the offending agent.¹⁶ Because continued treatment with an antineoplastic agent may be critical for achieving disease control, or even cure, desensitization protocols have been developed to safely re-introduce the antineoplastic agent after a hypersensitivity reaction has occurred. Premedication with corticosteroids, antihistamines, and/or leukotriene receptor antagonists can decrease hypersensitivity reaction risk.¹⁷ Desensitization entails administering the agent in incremental doses, ultimately delivering the same target dose over a longer time.^{18–19} This allows for a temporary state of tolerance by maintaining drug levels below the threshold concentration that would produce a symptomatic reaction.^{14–18–19}

The first rapid desensitization attempts in patients with a history of carboplatin hypersensitivity reactions resulted in repeated systemic reactions, and therefore extended inpatient desensitization regimens were developed.^{18–20–27} These latter desensitization regimens were conducted in the intensive care setting, with one-to-one supervision by specialized nurses and lengthy infusion times.²⁵ One of the first reported extended protocols included the administration of three infusion bags over 81 hours, which demonstrated antitumor activity and the prevention of further hypersensitivity reactions.²⁵ However, such protocols require extended hospital stays for each infusion cycle.

Castells and colleagues reported the first successful large-scale outpatient desensitization protocol for multiple antineoplastic agents.¹⁸ The agent for desensitization was administered over an average of 5.8 hours, with incrementally increasing concentrations over 12 steps.¹⁸ Although the protocol was effective, breakthrough reactions occurred in 33% of patients.¹⁸ These breakthrough reactions are challenging, as they may require discontinuation of an efficacious antitumor agent. Although multiple groups have

reported successful outpatient desensitization protocols, there are currently no national, standardized guidelines; as such, desensitization protocols and success rates vary across institutions.²⁸

Here, we evaluated the safety and efficacy of our outpatient 12-step desensitization protocol for patients who developed a hypersensitivity reaction to an antineoplastic agent.

METHODS

Patient Selection

After obtaining institutional review board approval, we retrospectively identified all adult patients who underwent desensitization following a hypersensitivity reaction to carboplatin, oxaliplatin, cisplatin, paclitaxel, docetaxel, trastuzumab, or liposomal doxorubicin at our institution from November 2016 to May 2021. Hypersensitivity reactions were diagnosed clinically and graded per Common Terminology Criteria for Adverse Events (version 5).²⁹ Attribution to the offending agent was determined based on the timing and clinical manifestations of the reaction. Per institutional practice, confirmatory skin testing was not routinely performed unless clinically indicated.²⁸ All patients were evaluated by an allergist and/or a physician experienced in hypersensitivity reactions.

Memorial Sloan Kettering Cancer Center Outpatient 12-Step Desensitization Protocol

Patients who had experienced a hypersensitivity reaction to an anticancer drug and required continued treatment with the agent were carefully counseled regarding our outpatient desensitization protocol. Consultation with an allergist was strongly advised. Patients were prescribed a home premedication regimen, such as oral prednisone (40 mg once a day) and montelukast (10 mg once a day) for 3 days before desensitization. Since β -blockers can attenuate the response to epinephrine, they were held as a precaution for 24 hours before desensitization in case epinephrine was needed for a severe reaction. The day of treatment, patients received intravenous dexamethasone 12–20 mg, diphenhydramine 50 mg, and ranitidine 50 mg or famotidine 20 mg. The premedication regimen was completed at least 30 min before initiation of the desensitization protocol.

Total infusion times for the drug undergoing desensitization vary based on the drug and target dose for each patient. An example of our outpatient 12-step desensitization protocol is outlined in [Table 1](#). In the example, the drug was delivered in three bags, and the infusion rate was increased four times per bag, for 12 total steps. The infusion time for steps 1–11 was 15 min per step. The first bag (steps 1–4) consisted of 1% of the total target dose. The rate of infusion was increased 2–2.5-fold per step, ranging from 2 to 20 mL/hour. If the infusion was tolerated without evidence of a hypersensitivity reaction, the remainder of the bag was discarded, and the second bag was started. The second bag (steps 5–8) consisted of 2.5% of the total target dose. The rate of infusion was increased 2–2.5-fold per step, ranging from 5 to 40 mL/hour. If this infusion was tolerated without evidence of a reaction, the remainder of the bag was discarded, and the third bag was started. The third bag (steps 9–12) consisted of 96.5% of the total target dose. The rate of infusion was increased 2–2.5-fold per step, ranging from 10 to 40 mL/hour for steps 9–11. If steps 1–11 were tolerated, the

Table 1 Example of the outpatient 12-step Memorial Sloan Kettering Cancer Center desensitization protocol

Bag number (total volume)	Percent of total dose	Step	Infusion rate for long infusion (mL/hour)	Infusion rate for short infusion (mL/hour)	Time per step (min)
Bag 1 (250 mL)	1%	1	2	4	15
		2	5	10	15
		3	10	20	15
		4	20	40	15
Discard remainder of bag. If no reaction, proceed to bag 2.					
Bag 2 (63 mL)	2.5%	5	5	10	15
		6	10	20	15
		7	20	40	15
		8	40	80	15
Discard remainder of bag. If no reaction, proceed to bag 3.					
Bag 3 (250 mL)	96.5%	9	10	20	15
		10	20	40	15
		11	40	80	15
		12	75	150	186 (long) 86 (short)

If no reaction in step 12, infuse remainder of bag at 75 mL/hour (long infusion) or 150 mL/hour (short infusion).
Total infusion time: 351 min (long infusion) or 251 min (short infusion).

remainder of the infusion was administered in step 12 at a rate of 75 mL/hour.

Patients without a breakthrough reaction during the first two desensitization cycles are eligible, at their clinician's discretion, to undergo a shorter 12-step desensitization protocol, which usually takes half the time to administer (Table 1). The short-infusion protocol is not used for treatments with a typical infusion longer than 86 min, such as oxaliplatin and paclitaxel 175 mg/m². Furthermore, due to drug concentration limits, some agents, such as paclitaxel and liposomal doxorubicin, require 500 mL in bag 3. For these 500 mL preparations, infusion rates for steps 9–12 are doubled (ie, 20–150 mL/hour for the long-infusion protocol and 40–300 mL/hour for the short-infusion protocol).

Hypersensitivity Reaction Characteristics

A hypersensitivity reaction was defined as any allergic or anaphylactic reaction attributed to the chemotherapeutic agent, regardless of grade, which was determined by Common Terminology Criteria for Adverse Events (version 5).²⁹ Patients who experienced a reaction received appropriate medical intervention per institutional standard practice.

Statistical Methods

Successful desensitization was defined as the completion of ≥3 desensitization cycles without severe hypersensitivity reaction or need for discontinuation. In general practice, the response to a chemotherapy regimen is assessed after three cycles. Therefore, the successful completion of three cycles allows the treating clinician to assess whether a chemotherapy regimen is effective and if it should be continued. Patients who had progression of disease or had to discontinue treatment due to a hypersensitivity reaction

before the completion of three cycles were considered unsuccessful.

The χ^2 test was used to analyze the association between prior signs of anaphylaxis and successful completion of treatment, with significance set at $p < 0.05$. The Mann-Whitney U test was used to analyze the association between the number of prior cycles and the successful completion of desensitization, with significance set at $p < 0.05$ and a two-tailed analysis used.

RESULTS

Patient Demographics

We performed a retrospective electronic medical record review of 186 patients who underwent an outpatient 12-step desensitization protocol after hypersensitivity reaction to an anticancer drug. Patient demographics are listed in Table 2. Median age was 59.5 years (range 26–87 years). One hundred and fifty-five (83%) were treated with platinum. Fifty-five (30%) were treated for colorectal cancer and 52 (28%) for ovarian cancer.

Desensitization Outcomes

One hundred and four patients (56%) completed ≥3 cycles of therapy during desensitization (Table 3). The median infusion time was 380 min (range 325–360). The median number of desensitization cycles was 3, with 694 cycles completed among all patients. Eighty-four patients (45%) discontinued treatment due to progression, and 41 (22%) discontinued the antineoplastic agent due to a breakthrough hypersensitivity reaction (Table 4). Among the patients who discontinued treatment due to breakthrough reactions, 20 (49%) underwent desensitization for oxaliplatin and 14 (34%) for carboplatin (Table 4).

Table 2 Patient characteristics

Characteristic	n=186
Median age, years (range)	59.5 (26–87)
Cancer type, n (%)	
Colorectal	55 (30%)
Ovarian	52 (28%)
Breast	22 (12%)
Pancreatic	16 (9%)
Endometrial	14 (8%)
Upper gastrointestinal tract*	12 (6%)
Other†	11 (6%)
Unknown primary	4 (2%)
Antineoplastic drug, n (%)	
Platinum	
Oxaliplatin	83 (45%)
Carboplatin	64 (34%)
Cisplatin	8 (4%)
Taxane	
Docetaxel	8 (4%)
Paclitaxel	8 (4%)
Liposomal doxorubicin	9 (5%)
Trastuzumab	6 (3%)
Median number of other drug allergies, n (range)	1 (0–11)
Median number of prior cycles containing drug for desensitization, n (range)	7.5 (0–40)
*Upper gastrointestinal tract cancers include bile duct, esophageal, gallbladder, gastric, and hepatocellular cancers.	
†Other cancers include lung, lymphoma, mesothelioma, parotid gland, and prostate cancers.	

Hypersensitivity Reactions during Desensitization

Seventy-nine patients (42%) experienced breakthrough hypersensitivity reactions during desensitization (Table 5), most during the initial desensitization cycle. Thirty-seven (47%) of these 79 patients experienced a grade 2 reaction and 12 (15%) experienced signs of anaphylaxis.²⁹ Only four patients (5%) required epinephrine to treat the reaction. A history of prior anaphylaxis to the drug was not associated with successful desensitization ($p=0.07$). Furthermore, successful desensitization was not associated with the number of prior cycles with the agent ($p=0.84$).

DISCUSSION

Summary of Main Results

Our outpatient 12-step desensitization protocol, which includes pretreatment with leukotriene receptor antagonist, antihistamine, and corticosteroids, as well as extended infusion times of 6–8 hours, resulted in successful desensitization in 56% of patients. Although there were no deaths associated with hypersensitivity reactions, 79 patients experienced a breakthrough hypersensitivity reaction

Table 3 Prior hypersensitivity reaction characteristics

Characteristic	n=186
Prior HSR grade, n (%)	
1	8 (4%)
2	67 (36%)
3	73 (39%)
4	19 (10%)
Unknown	19 (10%)
Prior HSR symptoms and signs, n (%)	
Erythema	71 (38%)
Urticaria	57 (31%)
Flushing	49 (26%)
Pruritus	45 (24%)
Dyspnea	39 (21%)
Prior epinephrine use, n (%)	19 (10%)
HSR, hypersensitivity reaction.	

and 41 discontinued treatment for this reason. Other studies have demonstrated success with risk stratifying patients based on the severity of their initial hypersensitivity reaction,^{30 31} an approach that may improve our protocol and outcomes.

Results in the Context of Published Literature

Ovarian cancer is very sensitive to platinum agents, which are associated with higher rates of hypersensitivity reaction with

Table 4 Desensitization outcomes

Characteristic	n=186
Median time in chemo unit, minutes (range)	380 (325–630)
Median number of desensitization cycles, n (range)	3 (1–28)
Successful completion of ≥ 3 cycles, n (%)	104 (56%)
Breakthrough HSR during desensitization, n (%)	79 (42%)
Reason for drug discontinuation, n (%)	
Progression of disease	84 (45%)
Hypersensitivity reaction*	41 (22%)
End of treatment	38 (20%)
Other	13 (7%)
Ongoing	10 (5%)
Drugs discontinued due to breakthrough HSR (n=41)*	
Oxaliplatin	20 (49%)
Carboplatin	14 (34%)
Cisplatin	2 (5%)
Paclitaxel	2 (5%)
Trastuzumab	2 (5%)
Liposomal doxorubicin	1 (2%)
HSR, hypersensitivity reaction.	

Table 5 Breakthrough hypersensitivity reaction characteristics

Characteristic	n=79
Median desensitization cycle for repeat HSR (range)	1 (1–8)
HSR grade	
1	6 (8%)
2	37 (47%)
3	31 (39%)
4	4 (5%)
Unknown	1 (1%)
Symptoms and signs	
Erythema	75 (95%)
Urticaria	57 (72%)
Flushing	49 (62%)
Pruritus	44 (56%)
Dyspnea	38 (48%)
Epinephrine administered	4 (5%)
Transfer to urgent care/emergency department	6 (8%)
Same-day rechallenge*	30 (38%)

*Rechallenged on the same day after breakthrough HSR occurred, following assessment by the treating clinician and appropriate medical intervention.
HSR, hypersensitivity reaction.

repeated exposure. While it is possible to switch to an alternative agent of the same class, life-threatening cross-reactions have been reported.⁷ Furthermore, the toxicity profile and clinical activity of the alternative agent may affect treatment decisions. Desensitization protocols, which vary across institutions, can be effective in reducing hypersensitivity reaction risk. Initial desensitization protocols required intensive care unit admission, with infusion times of up to 81 hours,^{20–26} which can be detrimental to patient quality of life.

Outpatient desensitization protocols were first developed after *in vitro* studies demonstrated the effectiveness of rapidly administering lowered doses of the desensitized agent in preventing mast cell degranulation.²⁷ The first rapid desensitization protocol, reported by Castells et al, demonstrated safety and efficacy among 413 patients.¹⁸ Their protocol entailed the administration of three solutions of the agent over 12 steps of incremental concentration increases, with a total infusion time of 5.8 hours.¹⁸ Most repeated hypersensitivity reactions occurred during the third desensitization cycle. Six percent of the repeated reactions were considered severe, but epinephrine was used in only one case.¹⁸ In another study by the same group, 72 of 77 patients who had experienced a prior hypersensitivity reaction to a taxane, including paclitaxel and docetaxel, completed desensitization without further reactions.³² Another analysis of 2177 desensitization cycles among 370 patients showed 93% of patients did not develop a hypersensitivity reaction or developed only a mild reaction, and only 7% developed a moderate-to-severe reaction.³⁰ All patients who

developed a hypersensitivity reaction completed treatment.³⁰ The desensitization protocol did not compromise the efficacy of carboplatin, with no statistically significant differences in overall survival between patients undergoing carboplatin desensitization and their respective controls.³⁰ A recent study by Barmettler et al evaluated the feasibility of an outpatient desensitization protocol in patients who had successfully completed inpatient desensitization without experiencing a grade ≥ 1 hypersensitivity reaction.³¹ There were no grade 4 reactions, and patients reported less disruption to their daily routines compared with inpatient desensitization.³¹ More recently, Castells' group analyzed the efficacy of their outpatient protocol at an outside institution.³³ The desensitization of 272 patients to 15 separate agents resulted in 141 breakthrough hypersensitivity reactions.³³ These studies illustrate the importance of implementing evidence-based outpatient desensitization processes across institutions, given the time commitment and disruption to patient life that inpatient desensitization requires, with infusions lasting up to 3 days. However, minimizing the risk of future reactions through optimization of desensitization protocols is essential to their success.

Strengths and Weaknesses

This study critically assesses the desensitization protocol used at our institution and provides valuable insights on its safety and efficacy, which can be translated to other institutional protocols. Per standard institutional practice, confirmatory skin testing was not routinely performed. While skin testing has been adopted at some institutions, several studies have shown its mixed utility due to the potential for false-negative results and conversion from a negative to a positive result; therefore, it is not part of our institutional practice.^{28 34 35} Reliance on clinical determination of the causative agent is a limitation of our study. Another limitation is the variability in premedication prescription and adherence. Although premedication is standardized within our protocol, there is some variability in prescription by providers and patient adherence to medications at home. Progression of disease is another variable that confounds our analysis, as many patients had to stop treatment due to progression before successful desensitization completion. Although these patients did not stop desensitization due to a repeat hypersensitivity reaction, we are unable to determine whether the desensitization was successful due to its premature completion. Furthermore, our study is limited by the data gathering issues inherent in retrospective chart review.

Our study examined the short-term outcomes of patients undergoing desensitization but did not assess the long-term progression-free survival benefits. To address this, a randomized prospective study is needed, with the control arm treated with an alternative antineoplastic agent.

Implications for Practice and Future Research

We demonstrated our institutional protocol for outpatient desensitization is effective in allowing patients to continue treatment; 41 (22%) stopped treatment due to a repeat hypersensitivity reaction and 84 (45%) due to progression of disease. Seventy-four (94%) of 79 repeat hypersensitivity reactions were mild or moderate; only four patients experienced a severe hypersensitivity reaction warranting treatment with epinephrine, and only six required urgent care transfer for monitoring. Despite our protocol's success, repeat

reactions were relatively common, and only 30 patients (38%) were rechallenged after experiencing a hypersensitivity reaction. Forty-one (22%) of 186 patients stopped treatment with the offending agent due to a repeat breakthrough reaction. In contrast, Castells' group validation included 370 patients, of whom only two required intramuscular epinephrine and none required discontinuation of the agent due to a hypersensitivity reaction.³⁰ The group used a 16-step, four-bag protocol lasting 400 min compared with our 12-step, three-bag protocol with a median duration of 380 min.³⁰ Furthermore, their group risk stratified patients based on the severity of the initial hypersensitivity reaction to determine the length of desensitization, whereas we used the same protocol for all patients. Both protocols were successful in preventing deaths associated with desensitization. Although our protocols are similar, the increased duration of their protocol may be a factor in the lower rate of repeat hypersensitivity reactions. While our multi-step desensitization protocol is successful in preventing hospitalization and death due to breakthrough reactions, more extended infusions for patients at high risk of future hypersensitivity reaction and risk stratification based on symptoms of initial hypersensitivity reaction may be warranted. Furthermore, future studies addressing the effects of desensitization protocols on survival outcomes are needed.

CONCLUSIONS

Our outpatient 12-step desensitization protocol facilitated the safe and successful desensitization to an antineoplastic agent among cancer patients with a history of hypersensitivity reaction to the specific agent. Our protocol is just one of several types used across institutions. Further research is needed to develop optimal desensitization strategies, building on existing protocols and possibly merging key aspects of the various methods.

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Original research

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