

Rapid desensitization for hypersensitivity reactions to chemotherapy agents

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Purpose of review

Hypersensitivity reactions (HSRs) to chemotherapy agents have limited their use for fear of inducing severe reactions or death. Alternative regimens may be limited by tumor sensitivity and the need to provide first-line therapy. Rapid desensitizations allow patients to be treated with medications to which they have presented a HSR. The purpose of this review is to highlight the indications and recent developments in chemotherapy rapid desensitization protocols.

Recent findings

Intravenous and oral rapid desensitization protocols are available for taxenes, platinum, doxorubicin, monoclonal antibodies and others. Candidate patients present mild to severe type I hypersensitivity, mast cell/IgE-dependent reactions, as seen with platinum. Anaphylactoid reactions, such as those with taxenes, can be treated with the same protocols. Repeat desensitizations in outpatient settings are well tolerated and allow patients to remain in clinical studies/trials. Breakthrough symptoms during desensitizations are less severe than the initial reaction and no deaths have been reported. Cancer remissions are similar to those for nondesensitized patients.

Summary

The use of rapid desensitization protocols for cancer patients with HSRs to chemotherapy depends on their demonstrated tolerability and efficacy in selected populations. Education of nurses, pharmacists, and oncology and allergy specialists is needed to improve their universal application as standard of care.

Keywords

carboplatin, chemotherapy, desensitization, monoclonals, platinum, taxenes

Introduction

Rapid desensitization is the induction of temporary unresponsiveness to drug antigens, thereby allowing patients to be treated with medications to which they have presented hypersensitivity reactions (HSRs). Gradual re-introduction of small amounts of drug antigens up to full therapeutic doses has been successfully achieved for over 50 years in patients with HSRs to antibiotics, using oral and intravenous protocols [1,2]. Unlike bacterial and viral vaccination, or classical allergen immunotherapy, in which weeks to months are required to provide immune protection, rapid desensitizations achieve full therapeutic doses without major side effects in a relatively short time – typically 4–12 h. Despite the clinical expansion and success of rapid desensitizations, the cellular and molecular inhibitory mechanisms inducing the temporary tolerization are still incompletely understood. An increasing number of cancer survivors and chronic rheumatology patients are exposed to repeated courses of chemotherapy and monoclonal antibodies, with increased sensitization rates. Although HSRs are rare, their treatment with rapid desensitizations provides patients with the unique opportunity to use first-line agents to which their tumors or chronic inflammatory conditions are responsive [3].

We reviewed the indications, methods and outcomes of rapid desensitization protocols for taxenes, platinum, doxorubicin and monoclonal antibodies in the last 5 years.

Rapid desensitization: principles and cellular and molecular targets

Beta lactam antibiotic desensitizations were started half a century ago to allow very sick patients presenting with type I hypersensitivity, mast cell/IgE-dependent reactions to be treated with their infection-sensitive agent without the induction of anaphylaxis [1]. Syphilis-presenting mothers with HSRs to penicillin were desensitized and successfully delivered healthy nonsyphilitic babies [1]. Clinicians were encouraged by this earlier success and numerous desensitization protocols have been generated since then for antibiotic and nonantibiotic drugs [2,4–6]. Despite their growing recognition and practical applications, all available clinical protocols are empirical and based on trial and error clinical experiences. Mast cells and basophils are thought to be the cellular targets, as mast cell mediators are released during HSRs to drugs [7] and skin test is positive in patients presenting with HSRs [8]. In addition, prolonged exposure is needed for sensitization and the generation of IgE antibodies [9]. In-vitro desensitization of human mast

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Abbreviation

HSR hypersensitivity reaction

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cells depletes syk, an upstream signal transducing molecule necessary for IgE signaling [10,11]. Naturally occurring syk-deficient basophils are unresponsive to drug antigens, indicating that syk is critical for activation and for desensitization [12]. In recent studies, Morales *et al.* [14^{*}] have shown that mouse mast cells deficient in STAT6 – a signal transducer and transcription activator involved in transcription of IL-4 and IL-13 – cannot be desensitized to IgE and antigen [13].

Desensitizations for anaphylactoid reactions, in which IgE cannot be demonstrated in patients presenting with symptoms of mediators release, have been empirically performed with similar success as for IgE-mediated desensitizations (see below). Patients reacting at first or second drug exposure present negative skin test, as seen in patients reacting to taxenes [15] or vancomycin [16]. The mechanism of desensitization of those reactions is unknown, as is the nature of the HSR.

Rapid desensitization for hypersensitivity reactions to taxenes

Paclitaxel is a widely used antineoplastic agent with activity against ovarian, breast and other solid tumors. Docetaxel is a semisynthetic taxane originally extracted from the needles of the European yew tree (*Taxus baccata*), whose antimetabolic activity is similar to that of paclitaxel [17].

A high incidence of HSRs were observed with paclitaxel in early clinical trials [15], with symptoms frequently occurring during the first course of therapy, within seconds to minutes of beginning the infusion. Slower infusion rates and premedication with H1, H2 antihistamine receptor antagonists and corticosteroids decreased the incidence of HSRs to less than 10% [18]. During HSRs to

taxenes, the activation of complement or the direct activation of mast cells/basophils by paclitaxel or cremophor has been postulated [19]. Attempts at using docetaxel (with no cremophor) in patients with paclitaxel HSRs have not proven universally successful and a subset of patients with taxene-responsive cancers need extensive premedications, slow infusions or desensitization to allow well tolerated treatments [17,20,21].

A standardized desensitization protocol developed by Feldweg *et al.* [22^{**}] at the Brigham and Women's Hospital (described in Table 1 [30]), was used to desensitize 40 patients who presented a HSR after the first or second infusion of paclitaxel or docetaxel for a total of 176 desensitizations [23,24^{**}]. The protocol has several advantages: the limited infusion time avoids neutropenia, the lack of severe side effects permits repeated desensitizations, and there is no need for premedication [20]. Symptoms of hypersensitivity to taxenes included immediate flushing, pruritus, urticaria, chest pain, hypotension and hypertension, gastrointestinal symptoms, musculoskeletal pain, dyspnea with O₂ desaturation and loss of consciousness. A slow infusion rate with additional antihistamines and corticosteroids failed in four patients. One patient switched to docetaxel developed a similar HSR. The solutions and protocols for the desensitization protocol are described in Table 1. All 40 patients completed their chemotherapy cycles, and breakthrough reactions, occurring in 12% of the desensitizations, were less severe than the initial reaction and did not preclude the completion of any treatment course (Table 2). The incidence of allergic diseases was 57%, which far exceeds the 15–20% reported for the general population [22^{**}]. An earlier review [25] of 19 patients with paclitaxel-induced HSRs found a statistically significant difference in the rate of hymenoptera venom

Table 1 Standard desensitization protocol using a total dose of 500 mg as an example

Total dose	500 mg	Solution concentration	Total dose in each solution (mg)		
Solution A	250 ml	0.02 mg/ml	5.0*		
Solution B	250 ml	0.20 mg/ml	50.0*		
Solution C	250 ml	2.00 mg/ml	500.0*		

Step	Solution	Rate (ml/h)	Time (min)	Administered dose (mg)	Cumulative dose infused (mg)
1	A	2	15	0.010	0.010
2	A	5	15	0.025	0.035
3	A	10	15	0.050	0.085
4	A	20	15	0.100	0.185
5	B	5	15	0.250	0.435
6	B	10	15	0.500	0.935
7	B	20	15	1.000	1.935
8	B	40	15	2.000	3.935
9	C	10	15	5.000	8.935
10	C	20	15	10.000	18.935
11	C	40	15	20.000	38.935
12	C	75	184.4	461.065	500.000
Total time = 5.82 h				Total dose infused = 500 mg*	

Reproduced with permission from Lee *et al.* [30].

*The sum of the doses in Solutions A, B and C equals 555 mg. Total dose infused is 500 mg.

Table 2 Characteristics of breakthrough reactions occurring during desensitization

	Carboplatin (11 pts)	Paclitaxel (6 pts)	Trastuzumab (1 pt)
Cutaneous			
Flushing	4	3	1
Pruritus	7	1	1
Urticaria	3	1	1
Cardiovascular			
Chest pain	1	2	
Tachy/bradycardia	2/0	1/0	
Hyper/hypotension	2/1	1/1	
Pulmonary			
Dyspnea	3		
Desaturation	1		
Gastrointestinal			
Abdominal pain	1	1	
Oropharynx			
Throat tightness	1		1

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sensitivity as compared with control patients. Patients with allergic conditions may be at higher risk for HSRs to taxenes. A novel agent that is solvent-free (abraxane) has been well tolerated in a patient who presented a HSR to paclitaxel [26*].

Rapid desensitization for hypersensitivity reactions to carboplatin

Carboplatin is an effective and well tolerated cytotoxic agent used as standard front-line chemotherapy for ovarian cancer [27]. For patients with platinum-sensitive recurrent cancer, with disease relapse after at least a 6-month disease-free interval, platinum-based chemotherapy remains the most active regimen. In addition to its clinical effectiveness, carboplatin has a low incidence of toxicity and limited nausea or vomiting with antiemetic therapy [28]. HSRs are uncommon during the initial courses, but the incidence of reactions increases to 27% in patients receiving more than seven cycles of carboplatin [9,29]. Symptoms of HSRs vary from cutaneous reactions, such as flushing and urticaria to life-threatening respiratory and cardiovascular compromise, including bronchospasm, chest pain and hypotension, with more than 50% of patients developing at least moderately severe symptoms [9]. HSRs to carboplatin often prompt its permanent discontinuation. HSRs to carboplatin are thought to be mast cell/IgE-mediated, as skin test performed on the volar surface of the forearm with a drop of a nonirritating concentration of carboplatin at 1–10 mg/ml is positive in over 80% of reactive patients [30,31] (Table 3). In 47 patients with 168 negative carboplatin skin tests performed before each course, 166 courses were uneventful and a HSR developed in only in two courses (4%) [31]. Markman *et al.* [32] performed 717 skin tests in 126 patients 30 min before each carboplatin treatment after the sixth cycle and found that 668 were negative and, of those, 10 were associated with HSRs (1.5% false-negative, 95% confidence interval

Table 3 Carboplatin skin test results

Skin test results	No. of patients (%)
Positive (total)	21 (80.8)
Prick (10 mg/ml)	1 (3.8)
Intradermal (1 mg/ml)	12 (46.2)
Intradermal (10 mg/ml)	8 (30.8)
Negative	5 (19.2)

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0.6–2.4%). Of the positive skin tests, six out of seven patients who attempted re-infusion presented with anaphylaxis. Skin test performed prior to the eighth cycle of carboplatin has been proposed as the most effective drug toxicity prevention method. Patients presenting with positive skin test are candidates for desensitization or an alternative regimen [33**].

Given that a carboplatin-based regimen is the standard therapy for platinum-sensitive recurrent ovarian cancer, eliminating carboplatin as a treatment option presents a significant disadvantage [34]. Death from re-introduction of platinum has been described [35]. Several protocols for re-introduction of carboplatin and other platinum have been developed [36,37*]. Risk factors for developing a HSR to carboplatin include the presence of previous allergic conditions. A study [38] of women treated for ovarian cancer with more than six cycles of carboplatin found that of 30 patients with a history of allergy, 40% developed HSRs to carboplatin, but of 53 without history of allergy, only 19% developed a HSR to carboplatin. Despite intense premedication with steroids and antihistamines, a slow infusion protocol induced side effects in 77% of 13 patients with severe HSRs to carboplatin [39*]. A 6-h rapid desensitization protocol was used to treat 20 patients with HSRs to carboplatin and positive skin test, who tolerated 80 desensitization courses with no side effects [37*]. Lee *et al.* [30] treated 54 patients over 162 desensitization courses with the standardized desensitization protocol described in Table 1 – the same as for taxene desensitization – with three solutions for 6-h and 12 steps [23**]. Skin test was positive in 80.8% of 21 patients (Table 3). Patients received a median of eight courses before developing their initial HSR, as observed in other studies [9,40]. The reaction profile was consistent with type I hypersensitivity [23**,29]. Most patients had their initial HSR during the infusion, with six patients experiencing symptoms within 15 min of the infusion, but no delayed reactions were observed. Cutaneous manifestations were present in 96% of the patients and extracutaneous in 77%. In contrast to patients presenting with reactions to paclitaxel, there was a low incidence of musculoskeletal pain (3 compared with 45%). Breakthrough reactions were mild, with no deaths (Table 4). Prolonged desensitization regimes have allowed one patient with ovarian cancer and a HSR to carboplatin at the tenth cycle to be treated

Table 4 Management of breakthrough symptoms for three patients receiving carboplatin desensitization

Breakthrough symptoms (BS)	Step in which symptoms occurred	Treatment of symptoms	Protocol modification for subsequent desensitization	Outcome
Pruritus	15 min into Step 12, 3rd inpt desens	Stopped infusion. Treated with diphenhydramine. Restarted infusion at Step 12. No further BS during infusion	Decrease rate of Step 12 to 60 ml/h. Total time of infusion on modified protocol = 6.6 h	No BS during subsequent desens. (two courses)
Flushing, dyspnea, mild desaturation	20 min into Step 12, 1st inpt desens	Stopped infusion. Treated with diphenhydramine and supplemental O ₂ . Restarted infusion at Step 12. No further BS during infusion	Added two intermediate steps between Steps 11 and 12. Intermediate Step 1 (Solution C at 50 ml/h × 15 min). Intermediate Step 2 (Solution C at 60 ml/h × 15 min). Total time of infusion on modified protocol = 6 h	No BS during subsequent desens. (two courses)
Flushing, pruritus, progressing to throat tightness, vital signs stable	45 min into Step 12, 2nd outpt desens	Stopped infusion. Treated with diphenhydramine, intramuscular epinephrine, intravascular hydrocortisone. Restarted at 40 ml/h for remainder of Step 12. No further BS during infusion	Increase volume of Solution C from 100 to 250 ml. Solutions A and B remain the same, at 100 ml. Total time of infusion on modified protocol = 5.8 h	No BS during subsequent desens. (one course)

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during three recurrences for a total of 56 cycles [41]. Successful oral desensitizations have been performed [42] in a series of patients with HSRs to carboplatin, cisplatin, paclitaxel and bleomycin.

Skin test after carboplatin desensitization: inhibition of skin mast cells

To determine the effect of desensitization on cutaneous mast cells, skin test has been performed before and after desensitization by Lee *et al.* [30] and others [36]. Skin test to carboplatin became negative after desensitization in patients who tolerated full doses of carboplatin through desensitization, indicating the inhibition of cutaneous mast cell reactivity. Whether this reflects the mechanism of systemic tolerization has not been studied.

Other platinum: cisplatin and oxaliplatin

Attempts at substituting cisplatin in carboplatin-sensitive patients has been described in five out of six patients, but no skin test was available to provide evidence of the sensitivity [43*]. In two patients with HSRs to cisplatin who presented with positive skin test, premedication with steroids and antihistamines did not prevent the anaphylactic symptoms and desensitization was performed [44].

Reactions to oxaliplatin have been described, including anaphylaxis [45*], and, in most cases, the HSR precludes the use of the drug and premedication is ineffective [46,47,48*]. Skin tests have demonstrated an IgE mechanism, and desensitization protocols have been used in several case reports, including two patients with colorectal cancer who presented with severe anaphylactic reactions [47,49*] and another patient who received a

slow 24-h infusion after developing a HSR during the sixth cycle [50].

Studies of IgE cross-reactivity among platinum drugs are needed but the role of rapid desensitizations is clearly established.

Platinum desensitizations in children

The use of carboplatin has been limited in children with unresectable low-grade glioma due to a high rate of HSRs to carboplatin and few studies have validated the use of alternative drugs [51*]. A series of nine patients with HSRs to carboplatin were treated with vinblastine weekly with an acceptable toxicity: efficacy ratio [51*], but no guidelines have been provided for children's desensitization to carboplatin. Children with type 1 neurofibromatosis develop optic tumors which are treated with carboplatin, and 30% develop HSRs after multiple exposures, which have been treated successfully with rapid desensitizations, with good tumor responses [52]. Children with astrocytomas develop similar rates of HSRs after exposure to several cycles of carboplatin, and desensitizations have been successful in six out of 26 children with HSRs [53]. Two children who received multiple desensitization cycles had stable remission of their astrocytomas [54]. A girl with optic glioma developed a HSR after nine courses of carboplatin and was successfully desensitized [55].

Rapid desensitization for monoclonal antibodies

HSRs to humanized monoclonal antibodies are rare but their frequency is increasing, as cancer survivors and chronic inflammatory disease patients are exposed to multiple courses of the same or similar agents [56*,57]. Substituting agents with similar efficacy profiles has been

performed, and a study [57] of seven patients who had HSRs to infliximab (Remicade) tolerated adalimumab well, but disease control did not follow. HSRs to rituximab (Rituxan) [58–60], to trastuzumab (Herceptin) [61–63] and to anti-TNF α monoclonal antibodies [56[•],64–66] have been described. Desensitizations have been reported for humanized monoclonal antibodies [67[•],68,69] in patients with reactions compatible with a type I HSR, in which a mast cell/IgE mechanism is postulated. Four patients with Crohn's disease were desensitized to infliximab, although the skin test was negative, and complications included serum sickness in two patients after desensitization [67[•]]. Two patients with Crohn's disease – one adult and one child – with anaphylactic symptoms were desensitized successfully with no complications [70]. Lee *et al.* [23^{••}] used the protocol described in Table 1 to desensitize patients to rituximab and trastuzumab. The initial reaction was severe in both cases and included anaphylaxis (Table 2). An IgE mechanism was demonstrated by positive skin test to a nonirritant concentration of trastuzumab. Breakthrough symptoms were less severe than the initial reaction and allowed the patients to complete their courses.

Rapid desensitization procedures: location and tolerability

In the Feldweg and Lee series [22,23^{••},30], all patients received their first desensitization in the intensive-care setting and once they had completed a desensitization with no or minimal side effects, repeated desensitizations were transitioned safely to the outpatient clinics with one-on-one nurse support. One patient desensitized to trastuzumab presented side effects during the first two initial desensitizations and was later transitioned to the outpatient setting, where she underwent eight more courses without side effects, with a modified protocol (Table 2).

Outcomes of desensitizations and cancer progression

Whether chemotherapy desensitizations are effective at tumor progression control or at inducing complete remissions has not been defined. In the Lee *et al.* series [23^{••}], of 26 patients receiving carboplatin desensitization for recurrent cancer, 10 (38.5%) had a radiographic response (partial or complete response) or over 50% drop in initial CA125 value, 11 (42.3%) had stable disease radiographically or CA125 response (<50% drop), and five (19.2%) had progressive disease after one or two cycles of carboplatin. Of three patients receiving paclitaxel desensitization for recurrent cancer, one had clinical response to therapy, one stable disease and one progressive disease. Of 16 patients receiving paclitaxel desensitization for newly diagnosed cancer, all (100%) achieved clinical remission, which is the expected rate for cancer patient

populations not receiving chemotherapy desensitizations. Acceptable objective response rates to therapy were also seen in 22 of 28 patients treated with a prolonged desensitization carboplatin infusion regime for severe HSRs to carboplatin [40].

Conclusions

Rapid desensitization protocols are available for the treatment of patients with cancer and chronic inflammatory diseases who present with HSRs. Candidate patients present mild to severe type I hypersensitivity, mast cell/IgE-dependent as well as anaphylactoid reactions. Symptoms include pruritus, flushing, urticaria, angioedema, respiratory and gastrointestinal distress, changes in blood pressure, including hypotension, and shock with anaphylaxis. Musculoskeletal pain is present in patients reacting to taxenes. Initial rapid desensitizations should only be performed in settings with one-on-one nurse–patient care and where resuscitation personnel and resources are readily available. After the first desensitization, well tolerated repeated desensitizations can be performed in the outpatient setting with similar conditions, to allow patients to remain in clinical studies. Breakthrough symptoms are less severe than the initial HSR and deaths have not been reported. Antihistamines and steroids with deceleration of the dose escalation improve the tolerability of desensitization protocols. Cancer remissions are induced by desensitization protocols at similar rates as for nondesensitized cancer populations.

Education of nurses, pharmacists and medical specialties providers is needed before rapid desensitization protocols for cancer and chronic inflammatory disease patients can be universally implemented as a standard of care.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 303–304).

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