



A new non-dilution rapid desensitization protocol successfully applied to all-grade platinum hypersensitivity

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Received: 23 January 2018 / Accepted: 2 August 2018
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Abstract

Purpose Desensitization is a safe alternative for patients with hypersensitivity reactions (HSRs) to platinum-based chemotherapeutic agents and widely used in real practice by employing stepwise administration of multiple serial dilutions of the culprit drugs. However, its labor-intensive nature has required a simpler protocol that is easier to prepare and perform.

Methods We performed an observational study of patients with platinum HSR who underwent a new non-dilution one-bag desensitization protocol. Premedication consisted of Montelukast as well as H1 and H2 blockers. The outcomes and safety profiles of a new protocol were assessed.

Results A total of 36 patients were recruited (oxaliplatin 23, carboplatin 9, and cisplatin 4) and the most common grade of HSR presented was grade 2 (61.1%), followed by grade 3 (25%), and grade 1 (13.9%). Of 175 desensitization procedures, all cases were successfully completed in re-administration of culprit chemotherapeutic platinum agents; 146 (83.4%) had no breakthrough reactions (BTRs) while 29 (16.6%) did. Most BTRs were mild reactions (grade 1, 51.7%) or moderate reactions (grade 2, 44.8%) of Brown's Scale. Although there was one case of asymptomatic mild hypotension (grade 3, 3.5%), categorized as severe reaction, dyspnea, desaturation, and anaphylaxis did not occur. The proportion of severe HSRs was significantly lower than that of initial HSRs (3.5% vs. 25%, $P=0.0167$).

Conclusions The new non-dilution desensitization protocol was safe and effective for re-administration of culprit platinum agents in patients with a history of HSRs. Therefore, this new protocol can be used as an alternative to existing protocols using multiple serial dilutions.

Keywords Drug hypersensitivity · Antineoplastic agents · Desensitization · Immunologic · Platinum · Drug-related side effects and adverse reactions

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00280-018-3662-0>) contains supplementary material, which is available to authorized users.

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Abbreviations

AUC Area under the curve
BTR Breakthrough reaction
HSR Hypersensitivity reaction

Introduction

Platinum-based agents, such as cisplatin, carboplatin, and oxaliplatin, are the major chemotherapeutic drugs used in the treatment of cancers in the gastrointestinal tract (gastric cancer, colorectal cancer, pancreatic cancer), genitourinary system (ovarian cancer, bladder cancer) and others (lung, head and neck, etc.) [1, 2]. Hypersensitivity reactions (HSRs) to platinum agents are not uncommon, especially in relation with repeated exposure for the treatment of colorectal cancer and ovarian cancer. Platinum-induced

HSR is generally known to be associated with IgE-mediated immediate response, ranging in severity from skin and respiratory symptoms to severe reactions such as hypotension and anaphylaxis [3, 4]. Therefore, repeated regular exposure to culprit agents is the strong risk factor for the recurrence of HSRs which enhances the immunologic memory [5]. Although more chemotherapeutic options are currently available, the second-line chemotherapeutics may not guarantee the survival benefit expected with the first-line agents in some cancers. Therefore, replacing with the second line due to HSR may result in a disadvantage for patients with those cancers to obtain the best therapeutic effect and an option to continue the first-line drugs with desensitization is needed, particularly in patients with colorectal cancer and ovarian cancers [6] since platinum-containing regimen resulted in a more favorable outcome in those malignancies [7, 8].

In general, desensitization is performed by the sequential administration of dilute solutions in multiple steps. Among various protocols, Castells et al. developed the standard 3-bag, 12-step protocol for carboplatin and cisplatin in gynecologic cancer patients in 2008 [9]. Thereafter, the same or similar protocols have been used for platinum-based anticancer drugs. However, the use of a diluted solution requires the additional effort of pharmacists and nurses, and surplus chemotherapeutic agents. In 2014, Li et al. reported outcomes of a four-step, one-solution desensitization protocol in patients with a mild HSRs to carboplatin/cisplatin [10]. However, it is not clear whether their protocol can be applied to those who experienced severe HSR such as anaphylaxis.

Here we developed a new simplified 12-step desensitization protocol with an undiluted solution and evaluated the outcomes of the new protocol.

Materials and methods

Study subjects

A retrospective observational study was done based on the desensitization monitoring records of patients with platinum HSR who underwent a new one-bag desensitization protocol without dilution from November 2015 to March 2017 at the Seoul National University Hospital. Inclusion criteria were (i) patients who had experienced symptoms compatible with immediate-type hypersensitivity reactions during drug infusion and (ii) request by their referred oncologist to be treated with the culprit chemotherapeutic agents. Exclusion criteria were (i) drug-induced hypersensitivity syndrome or drug reaction with eosinophilia and systemic symptoms, (ii) Stevens–Johnson syndrome, and (iii) toxic epidermal necrolysis.

The outcomes of desensitization such as the completion of infusion, the occurrence and timing of breakthrough reaction (BTR), the previous history of chemotherapy exposure, and skin test results were evaluated based on desensitization reports and medical records written by physicians and nurses. Our study was approved by the Seoul National University Hospital Ethics Committee (Approval number: 1705-035-852). Written consent was obtained from all patients following a detailed explanation of the study.

Skin test

The skin prick test and intradermal test were performed to measure the degree of sensitization to platinum. For the skin test, an undiluted platinum solution prepared for desensitization was used. The results were evaluated after 15 min and positive reactions were defined by a wheal size greater than 3 mm. A saline solution was used as a negative control and histamine was used as a positive control.

Desensitization protocols

We performed a new one-bag desensitization protocol with an undiluted solution. The dose was decided according to body surface area or area under the curve (AUC) of patients (oxaliplatin 85 mg/m², cisplatin 60–100 mg/m², carboplatin target AUC=5). The drugs were added to 150 or 200 mL according to the agent used (dextrose water 200 mL for oxaliplatin and carboplatin, normal saline 150 mL for cisplatin). The infusion line was primed with a platinum agent solution, which was gradually administered from an initial rate of 0.1 mL/h to a final rate of 150 mL/h (12 steps for oxaliplatin and carboplatin) or 450 mL/h (13 steps for cisplatin) by doubling of the infusion rate. Each step took 15 min before proceeding to the next step. A syringe pump (Terumo, Tokyo, Japan) was used to deliver accurate small amount of fluid for our desensitization protocol. Dextrose 5% in water was infused via a three-way stopcock in a rate of 10 mL/h to lower the concentration of the undiluted solution (Table 1). An H1-receptor antagonist (fexofenadine 180 mg or ketotifen 1.38 mg), H2-receptor antagonist (famotidine 10 mg), and leukotriene receptor antagonist (montelukast 10 mg) were orally administered before the desensitization. All desensitization procedures were carried out in the general inpatient wards.

Evaluation of HSRs and BTRs

The initial HSRs and BTRs during desensitization of the patients were classified as cutaneous (urticarial rash or

Table 1 An example of a 1-bag, 12-step desensitization protocol for oxaliplatin 120 mg

Step	Rate (mL/h)	Time (min)	Dose (mg)	Volume (mL)	Concentration after merging with side stream (mg/mL)*
1	0.1	15	0.0135	0.025	0.005332
2	0.2	15	0.0269	0.05	0.010559
3	0.5	15	0.0673	0.125	0.025643
4	1.2	15	0.1616	0.3	0.057697
5	2.5	15	0.3366	0.625	0.107701
6	5	15	0.6731	1.25	0.179501
7	10	15	1.3463	2.5	0.269251
8	20	15	2.6925	5	0.359002
9	40	15	5.385	10	0.430802
10	60	15	8.0775	15	0.461574
11	80	15	10.7701	20	0.478669
12	150	67.7	91.1497	169.3	0.504846

Oxaliplatin 120 mg/24 mL was reconstituted with 200 mL of 5% dextrose in water and the concentration of the solution was 0.5385 mg/mL

Dose (mg)=Rate (mL/h)×time/60 (h)×concentration (mg/mL)

*5% dextrose in water was infused as a side stream at a rate of 10 mL/h

angioedema), cardiovascular (hypotension, syncope, and dizziness), respiratory (dyspnea or laryngeal edema), gastrointestinal (abdominal pain and diarrhea), other systemic reaction, and anaphylaxis. The severity was assessed based on the scale proposed by Brown et al. [11]. According to Brown's Scale, Grade 1 (mild) reactions only involved skin or subcutaneous tissues, grade 2 (moderate) reactions involved other than skin reactions such as cardiovascular or gastrointestinal involvement, and grade 3 (severe) reactions were defined when hypoxia, hypotension, or neurologic symptoms also occurred.

Management of BTR during desensitization

The following post-HSR management guidelines were used depending on the severity of symptoms if symptoms of BTR appeared during desensitization. First, the infusion was stopped. If the hypersensitivity did not resolve after discontinuation, 4 mg of chlorpheniramine was administered intravenously. Hydrocortisone was administered intravenously (100 mg for grade 2 and 200 mg for grade 3) depending on the severity of the HSR. If respiratory distress due to bronchoconstriction was suspected, nebulized salbutamol (2.5 mg) was used. In grade 3 with hypotension, 0.5 mg of 1:1000 epinephrine solution was administered intramuscularly and repeated in 5 min if the blood pressure had not normalized. When the symptoms of hypersensitivity resolved, the desensitization procedure was supposed to be resumed at the interrupted stage in cases of grade 1–2 BTR or grade 3 BTR without

hypotension and at the previous step of the interrupted step in cases of grade 3 BTR with hypotension.

Statistical analysis

All measurements were expressed as mean ± standard deviation or percentage, and clinical characteristics were compared using *t* test and Pearson's Chi-square test. Statistical analysis was performed using SPSS version 21.0 (IBM Inc., Armonk, NY, USA) and a *P* value less than 0.05 was considered statistically significant.

Results

Baseline characteristics of patients

A total of 36 patients underwent rapid desensitization to platinum-based anticancer drugs between November 2015 and March 2017. The mean age was 60.83 ± 8.98 years, including 9 males and 27 females. Among the platinum-based chemotherapeutic agents, oxaliplatin was most commonly associated with HSRs ($n=23$), followed by carboplatin ($n=9$) and cisplatin ($n=4$). Among the participants, colorectal cancer was the most common ($n=18$) (Table 2). Regarding the purpose of the treatment, 33 patients underwent palliative chemotherapy and three underwent adjuvant and curative chemotherapy. With respect to the allergy history, two patients (5.6%) had both asthma and drug allergies. Seventeen patients (47.2%) underwent the skin prick test, all of which yielded negative results. The intradermal test

Table 2 Clinical characteristics of patients according to culprit agents

	Oxaliplatin (<i>n</i> = 23)	Cisplatin (<i>n</i> = 4)	Carboplatin (<i>n</i> = 9)
Indication	Colorectal cancer (18), advanced gastric cancer (1), pancreatic cancer (4)	Gallbladder cancer (1), naso-pharyngeal cancer (1), cervical cancer (1), breast cancer (1)	Ovarian cancer (6), cervical cancer (1), endometrial cancer (1), NSCLC (1)
Age (years)	60.26 ± 9.34	59.25 ± 9.43	63.00 ± 8.50
Male, <i>n</i> (%)	8 (34.8%)	1 (25.0%)	0 (0%)
Initial HSR grade, <i>n</i> (%)	Grade 1 (2, 8.7%) Grade 2 (13, 56.5%) Grade 3 (8, 34.8%)	Grade 1 (2, 50%) Grade 2 (2, 50%)	Grade 1 (1, 11.1%) Grade 2 (7, 77.8%) Grade 3 (1, 11.1%)
Cycle of initial HSR	6.30 ± 3.43	2.75 ± 0.96	2.38 ± 1.06
Total cycles when initial HSR occurred	9.35 ± 3.28	8.75 ± 8.92	8.75 ± 4.06
Remote previous chemotherapy exposure (%)	9 (39.1%)	2 (50%)	8 (88.9%)
Accumulated dose (mg/m ²)	675 ± 307.8	2385 ± 2326.58	207 ± 705.01
WBC	5321.74 ± 1805.43	4670.00 ± 979.05	5203.75 ± 1334.52
Eosinophil	190.12 ± 484.42	123.42 ± 114.89	278.39 ± 455.99
Lymphocyte	1895.30 ± 775.12	1951.50 ± 1236.71	1780.38 ± 1052.40

HSR hypersensitivity reaction, WBC white blood cells

results were positive in eight patients and the positive rate was 50% (7/14) for oxaliplatin, 50% (1/2) for carboplatin, and 0% (0/1) for cisplatin, with a total positive rate of 47.1% (8/17).

The most common grade of HSR presented was grade 2 (61.1%), followed by grade 3 (25%), and grade 1 (13.9%) (Supplementary Fig. 1(A)). The most frequently observed clinical manifestations were cutaneous (69.4%), respiratory (61.1%), cardiovascular reactions (19.4%) and anaphylaxis (13.9%), respectively (Fig. 1). We compared the timing of the initial HSR according to the presence or

absence of previous remote exposure to platinum anticancer drug. Of the 36 patients, 17 patients (47.2%) had no previous remote exposure to platinum anticancer drugs and 19 patients (52.8%) had a history of remote exposure to the same agent. While 13 of 17 patients (76.5%) without remote exposure had their first HSRs after the 6th cycle of chemotherapy. 14 out of 19 patients (73.7%) with remote exposure to platinum anticancer drug showed earlier occurrence of HSRs before the third cycle of chemotherapy (Fig. 2).

Fig. 1 The proportion of specific organ systems involved in initial hypersensitivity reactions and breakthrough reactions. HSR hypersensitivity reaction, BTR breakthrough reaction

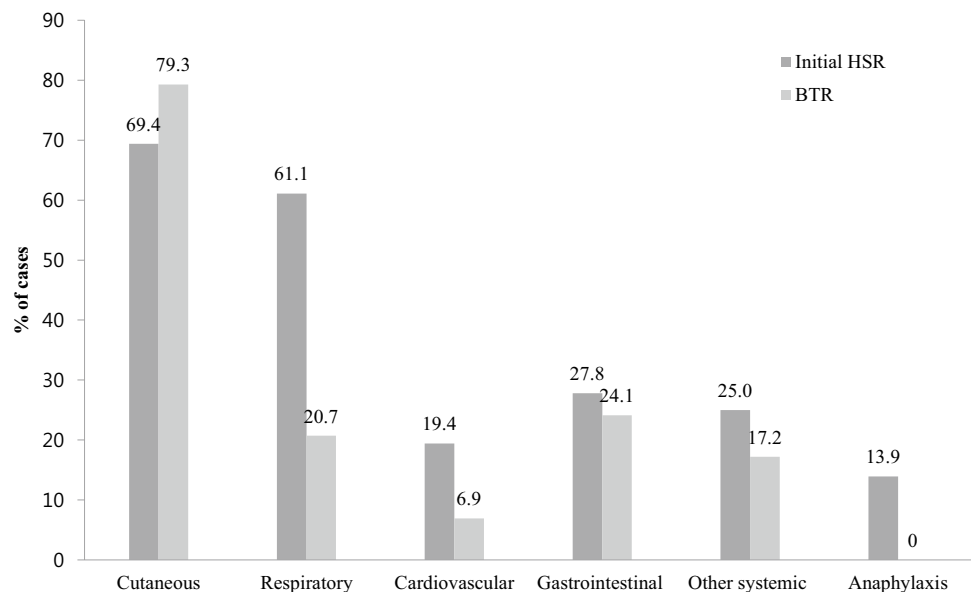
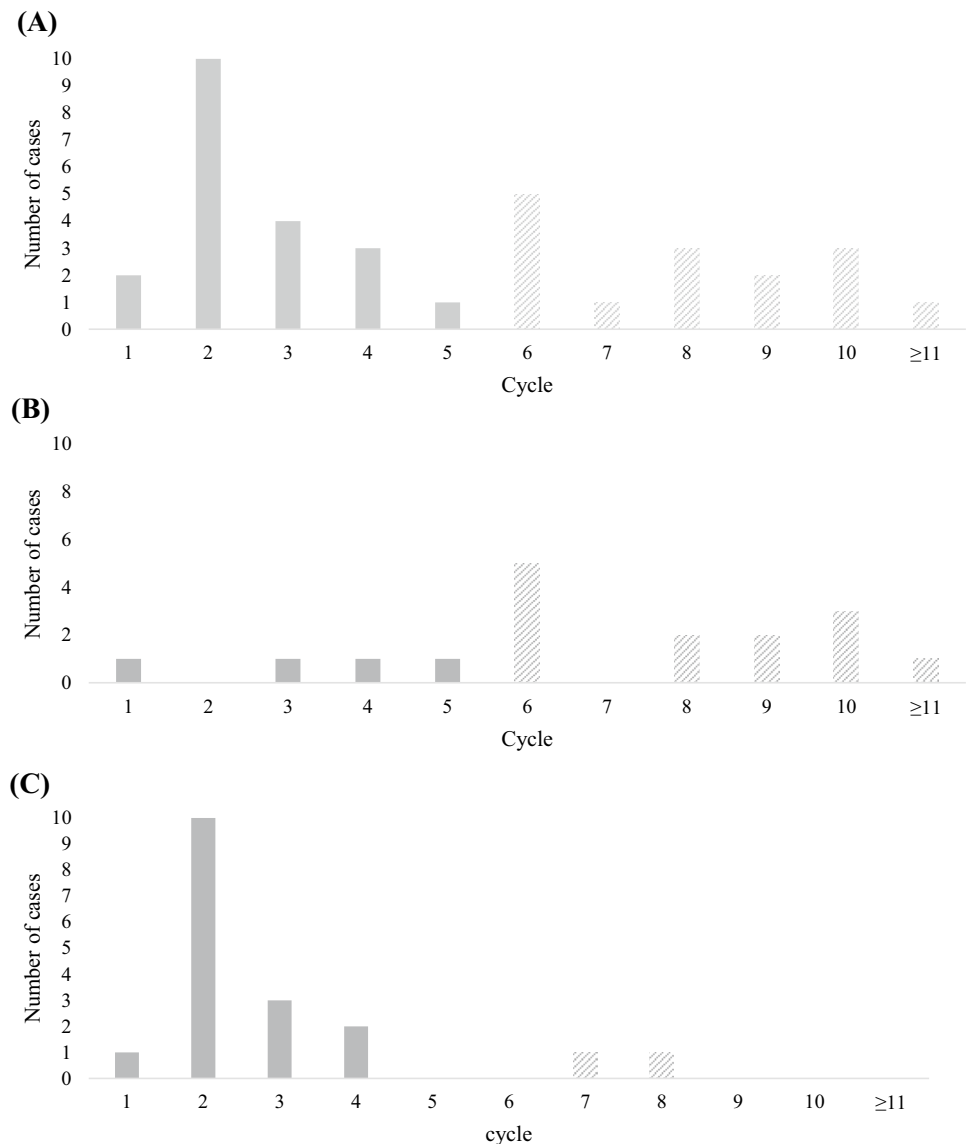


Fig. 2 The onset cycle of initial HSRs among patients with platinum hypersensitivity b. **a** Total ($n=36$). **b** No remote exposure to platinum anticancer drug previously ($n=17$). **c** Previous remote exposure to platinum anticancer drug ($n=19$).^aOne patient did not know the number of previous exposures. ^bThe striped pattern after the sixth cycle indicates that premedication was routinely administered



The outcomes of one-bag desensitization

A total of 175 desensitization procedures were performed according to a 1-bag, 12-step protocol (Table 1). Of these, 99 procedures (56.6%) were for desensitization to oxaliplatin, 63 (36.0%) for carboplatin, and 13 (7.4%) for cisplatin. The desensitization procedure was planned to be completed in 3.9 h but the median time for the completion of desensitization was 4.2 h (standard deviation 75 min) since some additional time was required to manage BTRs and observe progress. All desensitization procedures were successfully completed to the target dose. Of the 175 desensitization procedures, 146 cases (83.4%) completed desensitization without any BTRs while 29 cases (16.6%) of BTRs developed in 19 patients. BTR occurred only once in most patients (15 of 19 patients) while the remaining four patients experienced repeated BTRs (2, 3, 4, and 5 BTRs for each patient).

Among those with BTRs, grade 1 was the most common (15 cases, 51.7%), followed by grade 2 (13 cases, 44.8%) and grade 3 (1 case, 3.5%) (Supplementary Fig. 1(B)). Regarding affected organs, cutaneous reactions (23 cases, 79.3%) were the most common (Fig. 1). There were two cases of cardiovascular reactions; one was mild hypotension (within 30% of the baseline but systolic blood pressure was lower than 90 mmHg) without any significant clinical symptoms and the other case was dizziness without hemodynamic change. The proportion of severe HSRs, grade 3, was significantly reduced compared to those of initial HSRs (3.5% vs. 25%, $P=0.0167$).

In the case of oxaliplatin, BTRs occurred at median 11.00 (9.00–12.00) out of 12 steps, and most BTRs (74%) occurred after 10 steps of the protocol. Desensitization procedures were repeated in most cases, ranging from one to seven times, and most BTRs occurred in the initial cycle and

tended to decrease as the desensitization procedures were repeated (Supplementary Fig. 2).

Discussion

This study evaluated the outcomes of a new simple 12-step desensitization protocol with an undiluted solution of platinum-based chemotherapeutic agents. All patients completed desensitization without any life-threatening reactions in a shorter time compared to the multi-bag desensitization protocol. Hence, the dilution process is not essential for desensitization, and our study provides the efficacy and safety profiles of the one-bag desensitization.

Currently, desensitization protocols have been performed by sequentially administering diluted solutions in multiple steps to attain tolerance. A typical example is the 3-bag, 12-step protocol suggested by Castells et al. With this protocol, all cases of desensitization were completed without severe side effects but BTRs occurred in 32.6% of cases [9]. Similarly, Lee et al. used a similar 3-bag, 12-step protocol [12] and Hesterberg et al. applied a protocol involving two to three dilutions and eight to ten steps, depending on the results of the skin test [13]. In addition, Madrigal-Burgaleta et al. and Wong et al. used protocols involving 1–3 dilutions with 8–13 steps [14, 15]. Particularly, Nozawa et al. applied a desensitization protocol for colorectal cancer patients with oxaliplatin hypersensitivity in which they successfully administered a 1:10,000, 1:1000, 1:100, and 1:10 dilutions to the patients for 1 h each without changing infusion rate, followed by a 1:1 dilution for 4 h [16]. Park et al. also applied a 3-bag, 11-step protocol for Korean patients with oxaliplatin hypersensitivity [17]. Li et al. reported effectiveness and safety of four-step, one-solution desensitization protocol, but there are differences in the inclusion criteria compared with our study [10]. As a matter of fact, their study subjects were patients with a history of mild or low-risk, moderate immediate hypersensitivity reactions to carboplatin/cisplatin and those with moderate or severe reactions were excluded from the study while 41.7% of subjects of our study had severe reactions. In addition, it was composed of only four steps so it was close to graded challenge rather than desensitization. In conclusion, our protocol is the truly the first one-bag protocol.

Previously reported protocols presented 95–100% success rates; however, the incidence of BTRs was quite variable from 5 to 66.7% and the time spent for desensitization varied from 1.5 to 16 h [10, 12–15, 17–22] (Table 3). Compared with multi-bag protocol, the time required for our non-dilution one-bag was relatively shorter at 3.9 h. Although actual time for completion was 4.2 h in this study, the direct comparison could not be made since the exact time spent for other multi-bag protocol was not available in the literature.

In addition, our protocol also showed a modest BTR rate compared to other protocols. Of the 175 desensitization procedures, 29 cases of BTR developed in this study. Based on Brown's Scale [11], mild reactions occurred in 15 cases (51.7%), moderate reactions in 13 cases (44.8%) and only 1 severe case with mild hypotension (3.5%) in this study. Considering 6% of BTRs were a severe reaction in the 3-bag, 12-step protocol [9], the one-bag protocol is not inferior to the conventional multi-bag protocol. We additionally investigated BTRs according to the organ system. The most frequently observed symptoms were cutaneous reactions (79.3%, 23/29 cases) which was a higher proportion than in initial HSRs (69.4%). This was related to the relatively mild nature of BTRs compared to that of initial HSRs. In detail, the proportion of severe reactions such as cardiovascular reaction and respiratory reactions decreased during desensitization compared to the initial HSRs from 19.4 to 6.9% and 61.1–20.7%, respectively.

As mentioned earlier, most patients who experienced BTR had only one BTR but some patients showed repetitive BTRs. We regarded those patients with repeated BTRs as higher risk patients and applied an adjusted protocol with a gentle slope to two of them on the following cycles. An adjusted protocol was a 16-step protocol that gradually increased infusion rates by 1.6 times instead of doubling between steps. After applying this protocol, one patient did not develop any BTR and the other patient showed milder grade 2 BTR compared to the prior grade 3 BTR before modification. To assess the usefulness of the mitigated protocol, further studies are needed by applying this protocol to patients with higher risk.

The merit of our new desensitization protocol is that the labor requirement and the potential errors are reduced through simplification of desensitization procedure without multiple dilutions and changing bags. Therefore, our new protocol has the advantage of ease of use in real practice, especially in an outpatient setting.

Repeated exposure to platinum-based anticancer drugs increases the potential risk of HSRs. The frequency of HSRs increases during or after the eighth cycle of carboplatin chemotherapy [5] and during or after the seventh cycle of cisplatin chemotherapy [23]. In the case of oxaliplatin chemotherapy, hypersensitivity occurred on average around the 8.5th cycle. In addition, 28.6% of patients re-exposed to oxaliplatin developed hypersensitivity in earlier cycles [24]. In the current study, the majority of patients in the oxaliplatin group without previous remote exposure to oxaliplatin (57.1%) developed HSRs after the sixth cycle. On the other hand, the majority of patients with previous remote exposure to oxaliplatin (67%) developed HSRs before the third cycle. Our previous studies also have found that oxaliplatin hypersensitivity occurs at two peaks in Cycles 3 and 7 [25, 26]. Thus, these studies suggested that silent sensitization would

Table 3 The comparison of outcome with previous reports on platinum desensitization

Authors	Chemotherapeutic agents	Patients (cases)	Steps	Duration	Completion rate (%)	BTR rate (%) ^a	Severity of cases
Castells et al.	Carboplatin (60), paclitaxel (28), liposomal doxorubicin (5), doxorubicin (1), rituximab (3), cisplatin (3), oxaliplatin (1)	98 (413)	3 dilutions 12 steps	5.85 h	100	33	Grade 3: 6%
Lee et al.	Carboplatin (31), paclitaxel (22), docetaxel (1), trastuzumab (1), liposomal doxorubicin (1), uromitexan (1)	57 (255)	3 dilutions 12 steps	5.8 h	100	12.8	
Confino-Cohen et al.	Carboplatin	20 (80)	4 dilutions 4 steps	6 h	98.80	5	
Hesterberg et al.	Carboplatin	30 (106)	Skin test (−) → 2 dilutions 8 steps Skin test (+) → 3 dilutions 10 steps	6.35 h or 11 h	99	17.9	
Cortijo-Cascajares et al. ^b	Oxaliplatin	21 (53)	13 different concentrations	3–4 hr	100	11	Grade 2 reaction: 2% No grade 3 reaction
Madrigal-Burgaleta et al. ^b	Oxaliplatin (38), carboplatin (5), paclitaxel (136), docetaxel (2), cyclophosphamide (1), rituximab (5)	22 (189)	3 dilutions 10 steps	4.25 h	100	6	Grade 2 reaction: 29% Grade 3: 14% No death
Wong et al.	Oxaliplatin	48 (200)	1–3 dilutions In 8–13 steps	4.7–16 h	100	20	(per patient) Cardiovascular symptoms: 28% Respiratory symptoms: 28%
Li et al.	Carboplatin (13), cisplatin (5)	18 (95)	No dilution 4 steps	1.5 h (carboplatin) 2.25 h (cisplatin)	98.9	32	Moderate: 12% Severe reaction: 1%
Takase et al. ^b	Carboplatin	20 (83)	4 dilutions 4 steps	4 h	95	19	Grade 2: 50% Grade 3: 6.3% (hypotension)
Altwerger et al. ^b	Carboplatin	129 (788)	4 dilutions 4 steps	At least 3.5 h	93.8	(Per patient) 27.1	(Per patient) Grade 2, 3: 9%
Park et al. ^b	Oxaliplatin	12 (32)	3 dilutions 11 steps	3.95 h	100	66.7	Grade 3: 22.2%
Chung et al. ^c	Oxaliplatin, carboplatin, cisplatin	36 (175)	No dilution 12 steps	3.9 h	100	16.7	Grade 2: 44.8% Grade 3: 3.5%

^aPer case^bThe original CTCAE-based grades were converted to Brown Scale to compare with other studies.^cCurrent study BTR—breakthrough reaction

develop during previous remote exposure and contribute to the likelihood of hypersensitivity on re-exposure.

Our study has the following limitations. First, though potential error from preparation of dilution process may decrease, we cannot exclude the possibility of error risk in minute infusion with a syringe pump. When a minute volume is delivered by syringe, there is a concern that the correct volume could not be delivered in in vivo setting due to the rubber elasticity of the syringe and its interaction with the peripheral blood vessels in the body [27, 28]. However, most patients receiving chemotherapeutics desensitization often have to use a central line called chemo-port and the syringe pumps are proven to deliver accurate volumes up to 0.1 mL/h. Therefore, errors due to vessel compliance were not likely to be significant. The other limitation was the lack of skin test results in some patients and low sensitivity of the skin test. In our study, 17 patients (47.2%) underwent the skin prick test and 14 patients (38.9%) underwent the intradermal test. The skin prick or intradermal tests are representative diagnostic tests that evaluate IgE-mediated reactions, and are recommended as tools for risk stratification before starting desensitization [12, 29–32]. The sensitivity of the skin test was shown to be variable in several studies: carboplatin varies from 66 to 100%, oxaliplatin varies from 26 to 100%, and cisplatin was 66.7%. The concentration of a platinum solution for the intradermal skin test also varied in different studies (carboplatin 1 mg/mL, oxaliplatin 1–5 mg/mL, and cisplatin 1 mg/mL) [9, 11–14, 18, 32–37]. In our study, the sensitivity of the intradermal skin test was 50%. As we used undiluted platinum solution for the skin test, the concentration used for the intradermal test varied according to the body surface of each subject: the concentrations of carboplatin levels were 1.87 and 2.19 mg/mL (two cases), the median concentration of oxaliplatin was 0.59 mg/mL, and cisplatin 0.6 mg/mL. It is possible that the relatively lower concentration of platinum solution used for the skin tests may contribute to false negatives. Therefore, further studies are needed including more subjects using skin tests with higher concentrations of platinum anticancer drugs than our study.

In conclusion, a new desensitization protocol without dilution was successfully applied to patients with all-grade hypersensitivity to platinum-based anticancer drugs. This protocol showed safe outcomes in most patients with less time and labor compared to a conventional multi-bag protocol. Therefore, our one-bag desensitization protocol could be used as an alternative option to patients requiring re-administration of the culprit drug for previous drug hypersensitivity.

Acknowledgements This research was supported by a Grant from Ministry of Food and Drug Safety to the regional pharmacovigilance center in 2017.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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