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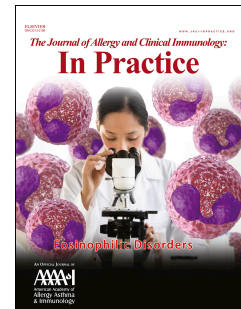
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Title: A one-bag rapid desensitization protocol for paclitaxel hypersensitivity: a non-inferior alternative to a multi-bag rapid desensitization protocol

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Disclosure

The authors declare that they have no relevant conflicts of interest.

Abstract

Background: Desensitization is used to safely continue treatment with a culprit drug in patients with drug hypersensitivity. Currently, a multi-bag protocol is widely used for rapid desensitization but performing desensitization procedure is labor-intensive as pharmacists and nurses need to prepare and administer diluted solutions. However, it has not been investigated whether dilution is essential for successful desensitization.

Objective: To investigate the efficacy and safety of a non-dilution, one-bag protocol in comparison to a conventional multi-bag protocol for desensitization of patients with paclitaxel hypersensitivity.

Methods: Patients who underwent paclitaxel desensitization between 2011 and 2018 were analyzed in this retrospective cohort study. The completion rate, time to completion, and occurrence and severity of breakthrough reaction (BTR) between one-bag protocol and multi-bag protocol were compared.

Results: A total of 211 desensitization procedures were performed, of which, 207 procedures (98.1%) were completed successfully. The administration time was significantly shorter in the one-bag protocol group compared to the conventional multi-bag protocol group (266.0 ± 149.3 min vs. 484.2 ± 178.6 min, $p < 0.05$) without differences in the completion rate (97.6% vs. 98.9%, $p = 0.645$), the incidence of BTR (16.1% vs 27.6%, $p = 0.778$), and the proportion of severe BTR (2.6% vs. 5.7%, $p = 0.134$).

Conclusions: A non-dilution, one-bag protocol is non-inferior to a multi-bag rapid desensitization protocol and can be a safe and effective option for paclitaxel desensitization.

Highlights box

1. What is already known about this topic?

- Rapid desensitization based on multi-bag protocol with serial dilutions is widely used in patients with immediate hypersensitivity reactions to chemotherapeutic agents but it is time-consuming and labor-intensive.

2. What does this article add to our knowledge?

- This article shows that one-bag paclitaxel desensitization protocol is non-inferior to the conventional multi-bag desensitization protocol in efficacy and safety.

3. How does this study impact current management guidelines?

- One-bag desensitization protocol may be a more practical alternative to multi-bag desensitization protocol and it can be easily implemented in real practice.

Keywords: Drug Hypersensitivity; Antineoplastic Agents; Desensitization, Immunologic; Paclitaxel

Abbreviations

HSR: Hypersensitivity reaction

IgE: Immunoglobulin E

BTR: Breakthrough reaction

SOCs: System Organ Classes

Introduction

Paclitaxel is an anti-cancer agent used in the treatment of various cancers, including ovarian cancer, breast cancer, and non-small cell lung cancer.¹ In the clinical trials, immediate hypersensitivity reactions (HSRs) occur in 30% of patients during or after infusion of paclitaxel.¹⁻³ Despite antihistamine and steroid pre-treatments, and slowing down the rate of infusion, HSRs still occur in up to of patients.^{1, 4, 5}

Taxanes are known to cause mainly non-IgE mediated allergic reactions and nearly 95% of patients with paclitaxel hypersensitivity experience HSRs at the first exposure.⁶⁻⁹ Related symptoms are usually typical manifestations of infusion reactions such as flushing, chest or back pain, hypertension, and presyncope, but some patients can also develop IgE-mediated allergic reaction or mixed reaction.^{1, 10} Paclitaxel induced HSRs commonly occur during drug administration and sometimes these reactions can lead to life-threatening consequences.^{11, 12} Therefore, it is recommended to avoid re-administration if severe infusion-related reaction occurs. However, in the case of anti-cancer drugs, the change in chemotherapy regimen may affect the patient's life expectancy due to the decrease in treatment efficacy. For those cases, desensitization therapy can be considered as an alternative option that enables safe re-administration of the culprit anticancer drug.¹³

Although various desensitization protocols have been reported, a 12-step administration method developed by Brigham and Women's Hospital Desensitization Program using 3-bags with serial ten-fold dilutions is currently the most widely used desensitization protocol.¹⁴ Since then a number of modified protocols designed to add advantages or local improvements have been developed.¹⁵⁻¹⁷ In vitro and in vivo models have shown that rapid drug desensitization inhibits the hallmarks associated with mast cell and basophil activation by starting at a subthreshold dose and by increasing the dose gradually with 15-30 minute intervals.¹⁸ However, its widespread use is limited by the increase in workload of pharmacists and nurses who need to additionally dilute the chemotherapy solution into three or more bags and timely change bags in the order of concentrations. However, there is little evidence suggesting that the process of administering a series of diluted solutions is essential to the

94 efficacious and safe desensitization. Currently, high-precision pumps enable precise infusion at a rate
95 of 0.1 mL/hr; with the aid of these pumps, it is theoretically possible to deliver lower doses to initiate
96 desensitization without dilution. To validate this concept, our group previously developed a one-bag,
97 rapid desensitization protocol without serial dilutions and reported its efficacy and safety in the
98 desensitization of platinum agents.¹⁹ However, it did not include cases desensitized by a multi-bag
99 protocol and no direct comparison was made. Likewise, two recent studies reported the safety and
100 efficacy of taxane desensitization by the one-bag protocol,^{16, 20} but no direct comparison was made
101 with a conventional multi-bag protocol.

102 The aim of this study was to investigate the efficacy and safety of a one-bag protocol by comparing it
103 with a conventional multi-bag protocol for paclitaxel desensitization.

Methods

1. Study design

A retrospective cohort study was performed on patients with taxane hypersensitivity who underwent paclitaxel desensitization from 2011 to 2018 at Seoul National University Hospital. In this study, immediate HSRs were defined as adverse reactions with onset during the infusion or within 1 hour after completion. Patients presenting with features of mast cell or basophil degranulation such as throat tightness, flushing, hypotension or hypertension, dyspnea, and chest or back pain were considered to exhibit HSR. Data were collected through retrospective review of patients' electronic medical records. The severity of immediate HSRs was graded based on Brown's classification²¹; Grade 1 reactions were limited to the skin or subcutaneous tissues, grade 2 reactions included respiratory, cardiovascular or gastrointestinal symptoms, and grade 3 reactions were defined as hypoxia, hypotension, or neurologic compromise. This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB number: 1705-035-852).

2. Desensitization protocols

A multi-bag protocol had been used from January 2011 to October 2015 and was replaced by a one-bag protocol without serial dilutions from November 2015. The multi-bag protocol was based on the 3-bag (100:1, 10:1 and 1:1) protocol starting at 2 mL/hr and increasing the dose rate by 2-2.5 times every 15 minutes (Table 1).¹⁰ The one-bag protocol started at 0.1 mL/hr using a high-precision syringe pump (Terufusion[®] Syringe Pump, Terumo, Japan) without dilution and the dose was increased by doubling the rate every 15 minutes. To ensure the delivery of very small amount of solution in a one-bag protocol, 5% dextrose water at a rate of 10 mL/hr was administered in a side stream throughout the entire process of desensitization (Table 1). In both protocols, an H1-receptor antagonist (fexofenadine 180 mg), an H2-receptor antagonist (famotidine 20 mg), and montelukast (10 mg) were administered as premedication. Additional corticosteroids other than what was included in a

chemotherapy regimen were not administered. The estimated time required for the administration of paclitaxel (200 mg) was 338 minutes for the 3-bag, 12-step protocol and 203 minutes for the one-bag, 13-step protocol.

3. Primary and secondary outcomes

Since the goal of desensitization was successful drug administration, the primary outcome was completion of drug administration. The secondary outcomes were decrease in the occurrence and severity of BTR, and reduction in time to completion. The time spent on desensitization was calculated from the start of administration to the end as described in the nursing record.

The BTR were characterized based on the organs involved, cycles in which it took place, and the steps in which it occurred. The severity of the BTR was evaluated based on Brown's classification.²¹ The organs involved in the BTR were categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) Terminology System Organ Classes (SOCs) classification.²² skin and subcutaneous tissue disorders (pruritus, rash and urticaria), respiratory, thoracic and mediastinal disorders (cough, dyspnea, hypoxia and rhinorrhea), gastrointestinal disorders (abdominal pain, nausea and vomiting), general disorders and administration site conditions (chest discomfort, feeling hot and pain), nervous system disorders (dizziness and paraesthesia), cardiac disorders (pulse rate increased), and vascular disorders (flushing and hypotension).

4. Statistical analysis

A chi-square test was used to compare the incidence and severity of BTR, and the completion rate of two protocols. In addition, multiple logistic regression analysis was conducted to evaluate the effect of sex, age, underlying disease, number of cycles, and protocol on the occurrence of BTR. The mean time spent on desensitization and the mean steroid dose used in pretreatment were compared using t-test. All measurements were expressed as mean $\pm$ standard deviation or percentages, and clinical

154 characteristics were compared using t-test and Pearson's chi-square test. Statistical analysis was
155 performed using SPSS version 25.0 (IBM Inc., Armonk, NY, USA) and p value less than 0.05 was
156 considered statistically significant.

Results

1. Baseline characteristics of the study subjects

A total of 211 desensitization procedures performed on 49 patients were included in the study. Of these, 24 patients underwent 124 one-bag protocol desensitization procedures and 25 patients underwent 87 multi-bag protocol desensitization procedures. The mean ages of patients enrolled in the one-bag protocol group and the multi-bag protocol group were 57.0 ± 10.6 years and 43.7 ± 15.9 years, respectively ($p < 0.05$). When comparing the underlying diseases for desensitization, ovarian cancer accounted for the largest portions of both groups with 13 cases (54.2%) in the one-bag protocol group and 11 cases (44.0%) in the multi-bag protocol group (Table 2).

The initial HSR to paclitaxel occurred predominantly during the first or second chemotherapy cycle (98.0%) except in one case where it was observed during the fourth cycle. Except for one patient with immediate HSR to docetaxel, all patients had immediate HSR to paclitaxel. The patient who had docetaxel hypersensitivity also developed grade 3 BTR during the first cycle of paclitaxel desensitization. The initial HSR grades were as follows: in the non-dilution one-bag protocol group, one patient (4.2%) had grade 1 HSR, 14 patients (58.3%) had grade 2 HSR, and 9 patients (37.5%) had grade 3 HSR. In the multi-bag protocol group, one patient (4.0%) had grade 1 HSR, 15 patients (60.0%) had grade 2 HSR, and 9 patients (36.0%) had grade 3 HSR. The proportion of severity did not differ between the two groups ($p = 0.933$).

2. Comparison of desensitization outcome

207 out of attempted 211 desensitization procedures were successfully completed, giving a success rate of 98.1%. There was no significant difference in the completion rates between the non-dilution one-bag protocol and the multi-bag protocol (97.6 vs. 98.9%, $p = 0.645$). Three cases of the one-bag protocol and one case of the multi-bag protocol were not completed. One of the unsuccessful one-bag protocol cases experienced grade 3 BTR at the first step and his oncology physician decided to

discontinue paclitaxel administration. The other two cases in the one-bag protocol group and the one case in the multi-bag protocol group had grade 1 or 2 BTR but paclitaxel treatment was ceased due to the lack of treatment response to paclitaxel.

Although the proportion of patients who experienced BTR at least once was not significantly different between the two groups (58.3% vs. 52.0%, $p = 0.656$), BTR incidence during desensitization procedures was lower in the non-dilution one-bag protocol than in the multi-bag protocol (16.1% vs. 27.6%, $p < 0.05$). In multiple logistic regression analysis of sex, age, underlying disease, number of cycles and protocol, significant associations were observed between age and the number of cycles to BTR incidence ($\text{Exp}(B) = 0.973$ and 0.878 respectively, $p < 0.05$). After correcting for the above factors, the incidence of BTR did not differ significantly between the two protocols ($p=0.778$). We also performed a non-inferiority test under the hypothesis that the BTR rate of one-bag protocol would be within 1% difference compared to the BTR rate of the multi-bag protocol. One-tailed test with a significance level of 0.1 showed the power of 81.2%, which attained statistical significance.

The grade 2 or higher BTRs were found in 11 procedures (8.9%) in the non-dilution one-bag protocol and 18 procedures (20.6%) in the multi-bag protocol ($p = 0.014$). There was one case (0.8%) of grade 3 BTR in the non-dilution one-bag protocol group while 3 cases (3.4%) had grade 3 BTR in the multi-bag protocol group (Figure 1).

3. Desensitization duration

The starting and finishing time of 172 desensitization procedures (110 procedures cases of the non-dilution one-bag protocol, 62 procedures cases of the multi-bag protocol) was detailed in the nursing records. The desensitization duration of the non-dilution one-bag protocol was 218 minutes shorter than that of the multi-bag protocol (266.0 ± 149.3 min vs. 484.2 ± 178.6 min, $p < 0.05$) (Figure 2). In order to exclude the time spent on BTR treatment, the duration of desensitization in cases without BTR was additionally assessed; the mean duration of uneventful desensitization procedures in the

one-bag protocol group was 192 minutes shorter than that of the multi-bag protocol group (242.6 ± 79.1 min vs. 435.0 ± 111.8 min, $p < 0.05$).

4. BTR occurrence pattern

Out of 27 SOCs, 'skin and subcutaneous tissue disorders' had the highest frequency in the non-dilution one-bag protocol group (60%) and 'general disorders and administration site conditions' was the most common in the multi-bag protocol group (48%). There were no significant differences in the organs involved during BTR between the two groups (Table 3). In the non-dilution one-bag protocol group, the frequency of BTR was highest during the first desensitization (37.5%) and gradually decreased as the cycles progressed. The multi-bag protocol also showed the highest frequency of BTR during the first desensitization (48.0%) but did not show a stepwise decrease after repeated cycles (Figure 3). In addition, BTR occurred predominantly toward the end phase of desensitization when the highest concentration of the drug was infused (Figure 4).

Discussion

This study directly compared the outcomes of non-dilution one-bag protocol desensitization to those of the multi-bag protocol in patients with paclitaxel hypersensitivity and showed for the first time that the clinical efficacy and safety of the one-bag protocol was non-inferior to the multi-bag protocol. In addition, the duration of one-bag protocol was considerably shorter making it an attractive alternative to the standard multi-bag protocol.

In a previous study, 36 patients had successfully completed 175 desensitization procedure with platinum drugs using the same non-dilution protocol.¹⁹ However, a direct comparison was not performed between the existing multi-bag protocol and the non-dilution one-bag protocol therefore it is not clear if the one bag protocol for platinum desensitization is equally efficacy and safe or not. Our study is unique in that we directly compared multi-bag protocol to a one-bag protocol in the same study center, minimizing other confounders and making the comparison more clinically relevant. Encouragingly we found that the non-dilution one-bag protocol was not inferior to the multi-bag protocol in terms of the rate and severity of BTRs and had comparable success rate of desensitization.

In 2008, Castells et al. reported 413 desensitization procedures including carboplatin, paclitaxel and doxorubicin in 98 patients using 3-solutions and a 12-step protocol described above.¹⁰ Of the 413 desensitization procedures, 111 procedures (27%) exhibited mild reactions and 24 procedures (6%) exhibited severe reactions. These rates are comparable to the rates of combined grade 1 and 2 reactions (24.2%), and grade 3 reactions (3.4%) in the multiple-bag protocol in our study (Figure 1). Currently, this protocol seems to be the most widely used desensitization protocol of anticancer drugs.

A one-solution protocol has also been previously reported for a patient with grade 2 cetuximab hypersensitivity via a five-step protocol.²³ In 2016, 58 cases of desensitization to carboplatin and 12 cases of taxane desensitization were performed via a one-solution protocol with only one case of BTR with pruritus.²⁰ In that study, taxane desensitization was performed using a solution diluted to 1 mg/mL. In 2017, one-solution desensitization procedures performed on 90 patients with HSR to anticancer drugs was reported¹⁶ and there was only one mild late reaction amongst 19 patients who

underwent paclitaxel desensitization. In that study, paclitaxel was diluted to a total volume of 500 mL (0.4 mg/mL for 200 mg of paclitaxel), the administration rate was initiated at 5 mL/hr, and the rate was gradually increased to 10, 25, 50, 75, 100, 150, and 175 mL/h every 15 minutes. The estimated time for completion without BTR was 252.3 minutes for the administration of 200 mg paclitaxel and this is 50 minutes longer than the estimated time based on our one-bag protocol (202.9 minutes for 200 mg paclitaxel).

In addition to the favorable outcomes of desensitization itself, the main strength of our one-bag protocol is the considerable reduction in the workload of pharmacists and nurses. The application of one-bag protocol reduces the preparation time compared to the multi-bag protocol by omitting dilution steps and it lowers the risk of anticancer drug exposure for nurses as the bags do not need to be changed.²⁴ The one-bag protocol can also minimize human errors that can occur during administration such as incorrect order of desensitization solutions, incorrect drug concentration or rate of infusion due to multiple bags.²⁵ Finally the stability of diluted solutions below the recommended concentrations, such as 100:1 or 1:1000, is not known. In fact, Vazquez-Sanchez et al. were unable to prove that carboplatin solution diluted to 0.02 mg/mL was stable²⁶. Whether the same can be applied to paclitaxel or not is unknown. On the other hand, the one-bag protocol eliminates this uncertainty as the non-diluted solutions are known to be stable.

In this study, BTR occurred somewhat higher than the previous studies of taxane desensitization. BTR occurred in 6.5% by Feldweg et al.⁹ and 21% by Picard et al.,²⁷ whereas in this study, BTR occurred at rates of 16.1% in the one bag protocol and 27.6% in the multi-bag protocol. The differences in protocols may account for this observation since the non-dilution one-bag protocol in our study had a relatively fast administration rate and the rate of increase at the later steps can influence BTR occurrence. Indeed, BTR occurred mainly toward the end phase of desensitization when the highest concentration of the drug was infused (Figure 4). Castells et al. suggested that the administration rate should not be increased by more than 2.0-2.5 times at 15 minutes interval.¹⁰ However, there may be different optimal conditions according to subjects' vulnerability and severity

and it is possible that the optimal protocol has not yet been established. In our cohort, most BTRs occurred in the latter steps in the multi-bag protocol but two BTRs also occurred at the first step in the one-bag protocol, perhaps due to the one-bag protocol starting at a higher concentration than the multi-bag protocol. Interestingly, Pérez-Rodríguez et al. had high completion rate considering that their initial administration was at a higher concentration but with a more gradual increase between steps compared to other protocols.¹⁶ It suggests that a slower increase may prevent BTRs. Therefore, more gradual increase than our current protocol may be an option for safer desensitization in selected cases, and it is possible that better desensitization outcomes can be achieved by optimizing the protocols further.

In addition to the desensitization protocol itself, it is also possible that skin test results or other environment factors such as patient-to-nurse relationship may also influence the outcome.^{16, 28} In this study, although the rate of BTR appeared to be lower in the one-bag protocol group, there was no significant difference when the incidence of BTR after age was corrected. Since the one-bag protocol group cohort was older than the multi-bag protocol cohort, it could be speculated that the lower rate of BTR in the one-bag protocol group was due to the age difference. However, there is no report in the literature that the incidence of taxane hypersensitivity or BTR varies with age, therefore the effect of age on BTR is yet to be determined.

Several studies suggested that risk stratification and selection of patients should be performed through skin testing before desensitization.^{9, 10, 16, 27, 29} However, positive skin test rates in patients with immediate HSR to taxane vary from 12% to 71% depending on the study population.^{17, 27, 30, 31} Therefore whether the skin test for taxane should be routinely performed or not remains unclear since a large proportion of paclitaxel hypersensitivity may be non-IgE mediated. A recent study showed negative drug provocation tests in 52% of taxane-reactive patients²⁵ and it means not all taxane HSRs are allergic. Non-allergic mechanisms include complement activation due to solvents such as Cremophor EL or Tween 80 as well as direct activation of immune cells by taxane itself.^{32, 33} In addition, paclitaxel sensitization could have developed due to prior sensitization by plant protein.

Either way, even if the skin test is confirmed to be positive, it is also known that paclitaxel can be safely injected through desensitization.³⁴ Otani et al. reported that paclitaxel can be safely administered by desensitization or challenge according to the severity of initial HSR instead of skin test.³⁵ In our study, since most cases were at least initial HSR grade 2, desensitization was applied to safely administer paclitaxel. In addition, antihistamines and steroid treatments need to be withheld prior to skin testing.³⁶ Therefore we have not routinely performed skin tests in this study but our data still support good safety and efficacy despite this limitation.

There are several limitations in this study. First, although this study included the sufficient number of subjects to draw a conclusion about the difference between two protocols, the outcomes of the one-bag protocol were retrospectively compared to those of multi-bag protocol, a historical control which had been substituted by the one-bag protocol. Even though two protocols were performed in a very similar conditions, i.e. by the same medical facility and staffs at a similar time, selection bias could not be ruled out due to its retrospective design and lack of randomization. Another main limitation of this study is that desensitization was applied without confirmation of paclitaxel allergy through skin test or provocation test for reasons outlined the above. The absence of a confirmed diagnosis of hypersensitivity by skin test or provocation test could have caused some degree of selection bias and contributed to overestimation in the efficacy and safety. Skin test positivity is a known risk factor for BTR occurrence during desensitization with taxane and the potential bias in BTR rate and severity cannot be ruled out if there was a difference in skin test positivity rates between the two cohorts. Therefore, taxane skin testing may be needed to verify the potential risk of BTR at baseline in the future study. On the other hand, this study looks at the safety and efficacy of one-bag protocol in 'real-life' situation where skin testing or provocation test are either impractical or difficult. Considering that desensitization is still recommended for subjects with grade 2 or higher HSR to paclitaxel and only one individual in each group had grade 1 HSR in this study, skin test positivity is unlikely to influence the requirement for desensitization or the findings. Nonetheless, further studies with more numbers and confirmation of HSR to taxane would be optimal to confirm the safety and effectiveness of the one-bag protocol.

325 In summary, this study demonstrates that non-dilution, one bag desensitization to paclitaxel is
326 equivalent both in efficacy and safety, and significantly reduces the time required for desensitization
327 when compared with conventional multi-bag desensitization. Therefore, this non-dilution one-bag
328 desensitization protocol can be widely used in patients with paclitaxel HSR.

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421 **Figure 1. The severity of breakthrough reactions during desensitization**

422 **Figure 2. Time spent on desensitization therapy according to protocols (expressed as mean $\pm$**
423 **standard error)**

424 **Figure 3. The number and severity of breakthrough reactions during desensitization according**
425 **to cycles of chemotherapy**

426 **Figure 4. The number of breakthrough reactions according to steps of desensitization**

Table 1. Comparison of two protocols for paclitaxel desensitization with target dose 200 mg. Upper: 3-bag, 12-step protocol, Lower: non-dilution one bag, 13-step protocol using a high-precision syringe pump with a 10 mL/hr side stream throughout the entire process of desensitization

Step	Conc (mg/mL)	Rate (mL/hr)	Time (min)	Volume per step (mL)	Dose per step (mg)	Cumulative dose (mg)
1	0.008	2.5	15	0.625	0.005	0.005
2	0.008	5	15	1.25	0.01	0.015
3	0.008	10	15	2.5	0.02	0.035
4	0.008	20	15	5	0.04	0.075
5	0.08	5	15	1.25	0.1	0.175
6	0.08	10	15	2.5	0.2	0.375
7	0.08	20	15	5	0.4	0.775
8	0.08	40	15	10	0.8	1.575
9	0.8	10	15	2.5	2	3.575
10	0.8	20	15	5	4	7.575
11	0.8	40	15	10	8	15.575
12	0.8	80	172.9	230.5	184.425	200

Step	Conc (mg/mL)	Rate (mL/hr)	Time (min)	Volume per step (mL)	Dose per step (mg)	Cumulative dose (mg)	Estimated Conc with side stream* (mg/mL)
1	0.8	0.1	15	0.03	0.02	0.02	0.0079
2	0.8	0.2	15	0.05	0.04	0.06	0.0157
3	0.8	0.4	15	0.1	0.08	0.14	0.0308
4	0.8	0.8	15	0.2	0.16	0.3	0.0593
5	0.8	1.5	15	0.38	0.3	0.6	0.1043
6	0.8	3	15	0.8	0.6	1.2	0.1846
7	0.8	6	15	1.5	1.2	2.4	0.3000
8	0.8	12.5	15	3.1	2.5	4.9	0.4444
9	0.8	25	15	6.3	5	9.9	0.5714
10	0.8	50	15	12.5	10	19.9	0.6667
11	0.8	100	15	25	20	39.9	0.7273
12	0.8	200	15	50	40	79.9	0.7619
13	0.8	350	25.7	150.1	120.1	200	0.7869

*Calculated by taking the rate of side stream 10 mL/hr of 5% dextrose in water into account with the infusion rates of main stream 0.8 mg/mL of paclitaxel solution (200 mg in 250 mL of 5% dextrose water) at each step. Conc: concentration

Characteristics	Non-dilution one-bag protocol (n=24)	Multi-bag protocol (n=25)
Indication of paclitaxel use	Ovarian cancer (13), non-small cell lung cancer (3), breast cancer (3), cervical cancer (1), and etc (4)	Ovarian cancer (11), non-small cell lung cancer (3), breast cancer (4), cervical cancer (4), and etc (3)
Age (years)*	57.0 ± 10.6	43.7±15.9
Male, N (%)	4 (16.7%)	5 (20.0%)
WBC (x10 ³ /mm ³)	8.7±4.0	6.9±4.3
Eosinophil (%)	3.3±3.0	3.8±4.2
Lymphocyte (%)	22.4±12.0	23.0±9.2
Initial HSR grade	2.3±0.5	2.3±0.5
Dose of dexamethasone used in the pretreatment (mg)	21.8±14.0	28.5±14.5
Dose of paclitaxel used in desensitization (mg)	244.0±94.5	241.9±58.9
Total desensitization cycles*	5.2±2.9	3.5±2.0

Table 2. Characteristics of patient population

*When compared by t-test, *P*-value <0.05

437 **Table 3. Comparison of System Organ Classes involved in BTR**

System Organ Classes	One-bag protocol (20 procedures)	Multi-bag protocol (25 procedures)
Nervous system disorders	1 (5%)	5 (20%)
Depressed level of consciousness	1	0
Dizziness	0	3
Paraesthesia	0	2
Cardiac disorders	2 (10%)	3 (12%)
Heart rate increased	2	3
Vascular disorders	7 (35%)	10 (40%)
Flushing	5	7
Hypotension	2	3
Respiratory, thoracic and mediastinal disorders	4 (20%)	4 (16%)
Cough	0	1
Dyspnoea	3	2
Hypoxia	1	0
Rhinorrhea	0	1
Gastrointestinal disorders	0 (0%)	5 (20%)
Abdominal pain	0	1
Nausea	0	3
Vomiting	0	1
Skin and subcutaneous tissue disorders	12 (60%)	6 (24%)
Hyperhidrosis	1	1
Pruritus	8	3
Rash	2	0
Urticaria	1	1
General disorders and administration site conditions	11 (55%)	12 (48%)
Chest discomfort	8	11
Feeling hot	2	1
Pain	1	0

438

Figure 1

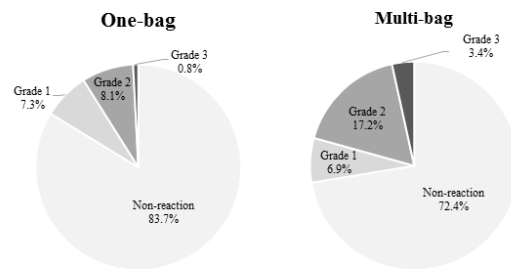


Figure 2

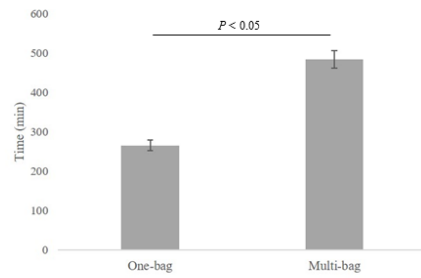


Figure 3

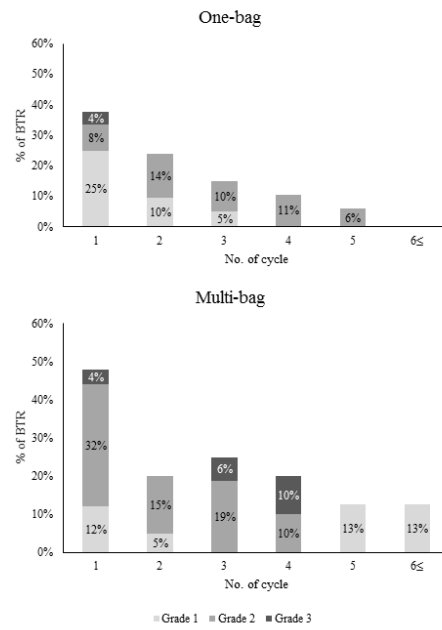


Figure 4

