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REVIEW

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Single-Bag Rapid Drug Desensitization: An Alternative to Multiple-Bag Desensitization Protocols

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ABSTRACT

Rapid drug desensitization (RDD) is a procedure that provides temporary tolerance to chemotherapy drugs for appropriate patients who experience hypersensitivity reactions (HSRs), allowing them to continue their treatments. Due to the labor-intensive and time-consuming nature of the commonly used multiple-bag RDD procedure, there is a need to develop an alternative protocol. In this article, we have compiled the results of a different clinical approach, the one-bag RDD procedure, in various patient groups.

Keywords: Desensitization, drug hypersensitivity, chemotherapeutics, biologics, neoplasms

INTRODUCTION

Hypersensitivity Reactions to Drugs

Immunologically, hypersensitivity reactions (HSRs) to drugs are classified into four types based on the Gell and Coombs classification: Type 1: IgE-mediated reactions, Type 2: cytotoxic reactions (immune hemolytic anemia, immune thrombocytopenia, immune granulocytopenia, vasculitic syndromes), Type 3: immune complex reactions (serum sickness), and Type 4: T cell-mediated reactions (contact dermatitis, maculopapular exanthems, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) (1,2).

Hypersensitivity Reactions with Chemotherapeutic and Biological Agents

In recent years, there has been a growing incidence of HSRs to chemotherapeutic and biological agents due to the increasing use of these therapies, which poses a significant barrier to the standard treatment of cancer patients. Chemotherapeutic and biological agents can induce early and delayed-type hypersensitivity reactions through the mechanisms described by Gell and Coombs (1).

Although chemotherapeutics account for only 5% of HSRs, they have been underestimated by oncologists due to the underreporting of mild reactions (3). Among chemotherapeutic agents, platinum-based and taxane-based agents are the most common causes of hypersensitivity reactions. It is believed that reactions with platinum-based agents often occur through a type 1, IgE-mediated mechanism, and their frequency increases with increased exposure. Both the frequency of positive skin tests and an increase in positive skin test results after repeated exposure support this data. Additionally, T cell-mediated reactions have been identified (4).

Taxane-based agents generally cause hypersensitivity reactions that occur during the first or second infusion (95%) and severe reactions occur within the first few minutes. Most likely, emulsifying agents added to the formulation of these drugs (Cremophor EL and/or polysorbate) are responsible for most HSRs. However, in some cases, positive skin tests have suggested the presence of an IgE-mediated mechanism in individuals' sensitive to certain plants involved in drug production (5).

With biological agents being a significant part of personalized therapy, HSRs associated with these agents have

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also increased. Acute infusion reactions, cytokine release syndrome, type 1 reaction (IgE, non-IgE), mixed reaction, serum sickness, and type 4 reaction have been described with these agents. Although most immediate-type reactions are mediated by IgG ADA antibodies, some immediate hypersensitivity reactions are caused by IgE-mediated mechanisms as well. In cases where there is no alternative treatment option available, desensitization should be considered for some types of HSRs such as cytokine release syndrome or type 1 reactions, or mixed reaction and milder forms of type 4 reaction (maculopapular rash or fixed drug eruption etc.) (6).

In cases of drug related HSRs, the usual course of action is to discontinue the implicated drug. However, when it comes to chemotherapeutic agents and biologicals, the decision to halt treatment is not easily made. This is because alternative drugs are generally more toxic and less effective. Consequently, this situation can lead to significant morbidity and mortality for patients. If the implicated drug remains the best option for treatment and/or if alternative drugs are deemed inadequate, desensitization for the responsible drug represents a viable treatment strategy (6-9).

DRUG DESENSITIZATION

Desensitization is the process of providing a temporary tolerance in which the treatment dose is reached by giving increasing doses of the implicated drug at certain time intervals. The tolerance developed is specific to the respective drug and will persist as long as the patient continues taking it (7,8).

The desensitization method has been applied worldwide for over 20 years, utilizing various protocols, but generally relying on the gradual increase in infusion rates and serial 10-fold dilution solutions to enhance the tolerance of the implicated chemotherapeutic agent or biologicals or other injectable drugs. When administered at low doses, the culprit drug binds monomerically to the FcER1 cross-linking site on mast cell and basophil surfaces, altering the allergen specific IgE/receptor interaction and rendering the cells unresponsive to the implicated drug (10).

Desensitization is contraindicated if there is an appropriate and effective alternative treatment for the patient. Desensitization is also contraindicated for severe cutaneous drug HSRs such as DRESS, SJS/TEN, AGEP and type II, type III reactions. Moreover, unstable underlying diseases (such as asthma, COPD, heart failure), use of beta-blockers or ACE inhibitors, or occurrence of more serious HSRs during the desensitization process pose a risk (9,11).

Identification of potential risk factors before and after making the decision for desensitization with the relevant agent can be instructive in determining the correct premedication and desensitization protocol and preventing and/or managing potential breakthrough reactions.

Skin Tests

Skin tests are the primary diagnostic method for assessing the risk of HSRs in patients. They are used more frequently for platinum group chemotherapeutics than other agents. Skin tests are performed for diagnosis, prevention, risk classification, and evaluation of cross-reactivity (9). Although it is recommended that skin tests be conducted 4-6 weeks after a reaction, shorter intervals may be necessary for chemotherapeutic and biological agents, leading to potential false-negative results (12). However, with repeated applications, skin tests can become positive (5,13). Alongside skin tests, other biomarkers such as specific IgE (sIgE), basophil activation test (BAT), soluble FcεRI and total IgE have also been under investigation for detecting sensitivity (14,15).

Premedication

The selection of drugs for premedication is generally based on the symptoms experienced by the patient during previous HSR. In addition, the manufacturer's recommendations for premedication should be taken into consideration for the implicated drug. Prior to RDD, H1 and H2 antihistamines can be used for cutaneous symptoms, aspirin for flushing, montelukast for bronchospasm, paracetamol for fever, and steroids for systemic symptoms (6,9,16). While it may not always be possible to prevent real IgE-mediated allergic reactions with premedication, it has significantly reduced the frequency of HSRs to taxanes to 2-4% (17).

Desensitization Protocols

Desensitization procedures are carried out using various protocols, starting from very low doses of the implicated agent and gradually increasing the dose. When the variations in premedication practices are added, as well as the modifications made after BTRs and the differences between local resources, it can be said that there is quite a variety of protocols (6,9,18).

The desensitization procedure is commonly used for chemotherapeutics and biological drugs. Desensitization with multiple bag protocols varying dilution and steps, depending on the patient's risk classification for chemotherapeutics and biological agents, have been proven effective in numerous cases (8,19). However, a three-bag, 12-step protocol developed by Brigham and Women's Hospital (BWH), Massachusetts General Hospital, and Ramon y Cajal University Hospital has become the most widely accepted protocol for treatment including in our own practice (7,20-22). In these studies, severe breakthrough reactions (BTRs) occurred in less than 1% of cases, and desensitizations were successfully completed in over 99% of cases (5,7,8). However, due to the intensive effort and time required by commonly used multi-bag desensitization procedures, there is a growing need for alternative protocols leading to increased interest in single-bag desensitization.

ONE-BAG PROTOCOLS

The time-consuming and labor-intensive nature of multiple bag protocols has led to the need for alternatives. The emergence of high-precision automatic pumps capable of infusing very small drug doses at rates as low as 0.1 mL/hour, which were previously achievable only through serial dilution, has made it possible to use one-bag concentration protocols without the need for additional dilution solutions. While the one-bag protocol saves time and effort, questions about safety and efficacy have arisen, leading to increased interest in this area with each new study (Table I).

In the majority of the literature, the preference for 3-bag 12-step protocols is evident, while studies ranging from 4 to 17 steps exist for one-bag protocols (23-33). In 2014, Li et al. have reported conducting 4-step desensitization in four patients with a mild history of low to moderate risk against carboplatin and cisplatin; however, their study faced criticism due to its closer resemblance to graded challenge in terms of step numbers and uncertainty regarding its applicability for patients experiencing severe HSR such as anaphylaxis (23). In 2016, Vidal et al. successfully completed all 58 desensitization procedures without BTR in a series of twelve patients with mostly severe initial reactions using a one-bag sixteen-step protocol (24).

In a study by Chung et al. in 2018, including patients with moderate to severe initial reactions, a 1-bag 12-step protocol led to the development of BTR in 17% of cases, with one being grade 3; nevertheless, it was successfully completed in 100% within an average of 3.9 hours. The limitation of the study was the inability to perform skin tests and its low sensitivity (25). In another study conducted in the same year on 90 patients, a single-bottle nine-step protocol resulted in the successful completion of 487 out of 490 desensitization procedures (99%), with BTR observed in only 5%, most commonly associated with platinum-based agents (26). The limitations were noted as the absence of skin tests and drug provocation testing. However, it was emphasized that proper medications and premedication are beneficial in preventing BTRs.

In 2020, Lee et al. reported that the one-bag 13-step protocol was as safe as the three-bag 12-step protocol in a group of patients with similar initial reaction severities (27). In another study conducted one year later, which included relatively high-risk patients and had a high rate of skin testing, the results of a one-bag protocol and three-bag protocol were compared. As a result, it was reported that there was no significant difference in the severity of BTRs in desensitization procedures completed with equal success rates (28).

In another study including 228 patients in 2022, it was reported that BTR occurred in 26% of the 1143 desensitizations, while all desensitizations were successfully completed in 99% of the cases (29).

In 2023, Vazquez-Revuelta et al. reported that out of the 263 desensitizations conducted in 65 patients, there was no BTR in 79%, with only grade 3 BTR observed in two patients. However, they stated that all RDD procedures were successfully completed (30).

Another study published in 2023 reported that all 130 RDD procedures conducted using a one-bag-16-step protocol were successfully completed, with BTR observed in 23%, all being of grade 1 severity (31). As mentioned previously, Vidal et al. similarly, reported that 58 RDD procedure conducted with a 16-steps protocol were completed without the observation of BTR (24). In contrast, Vetter et al. reported in their 2019 study that although none were serious, BTR occurred in 61% of the RDD procedures conducted with a one-bag 17-step protocol, requiring a switch to a three-bag protocol in five patients to complete subsequent desensitizations (32).

Table I: Single-bag rapid drug desensitization studies.

Authors, year (Ref no), N: patients (RDDs)	Agents	Protocol	Patients-Initial rx characteristics	BTR characteristics	Completion rate	Duration
Li et al. 2014 (23) 18(95)	Carboplatin:13 Cisplatin:5	1BP-4S	Initial HSR (*institutional) Mild: 9 (50%) Moderate low-risk: 9 (50%)	Mild: 19% Moderate: 12% Severe: 1%	99(94/95)	1.5 h (carboplatin) 2.25 h (cisplatin)
Vidal et al. 2016 (24) 12(58)	Carboplatin:8 Paclitaxel:2 Docetaxel:2	1BP-16S	Initial HSR (†institutional) Mild: 3 (25%) Severe: 9 (75%) ST-positive: 7 ST-negative: 5	BTR rate: 0%	100	ND
Chung et al. 2018 (25) 36(175)	Oxaliplatin:23 Carboplatin:9 Cisplatin:4	1BP-12S	Initial HSR (Brown) Grade I: 5 (14%) Grade II: 22 (61%) Grade III: 9 (25%) 17 completed ST ST-positive: 8 of 17 ST-negative: 9 of 17	BTR rate: %17 Grade I: 9% Grade II: 7% Grade III: 1%	100	3.9 h
Perez-Rodriguez et al. 2018 (26) 90(490)	Oxaliplatin:30 Carboplatin:16 Cisplatin:3 Paclitaxel:19 Docetaxel:6 Cetuximab:5 Rituximab:6 Other:8	1BP-9S	Initial HSR (Brown) Grade I: 33 (35%) Grade II: 49 (53%) Grade III: 11 (12%) 47 completed platin ST ST-positive: 34 ST-negative: 13	BTR rate: 5.3% (88% of platin desensitizations) Grade I: 3% Grade II: 2% Grade III: 0%	99(487/490)	ND
Lee et al. 2020 (27) 1BP: 24(124)	Paclitaxel	1BP-13S	1BP initial HSR (Brown) Grade I: 1 (4%) Grade II: 14 (58%) Grade III: 9 (38%)	1BP BTR rate: 16% Grade I: 7% Grade II: 8% Grade III: 1%	98% (121/124)	4.4 ± 2.5 h (4.1 ± 1.3 h for desensitizations without BTR)
3BP: 25(87)		3BP-12S	3BP initial HSR (Brown) Grade I: 1 (4%) Grade II: 15 (60%) Grade III: 9 (36%)	3BP BTR rate: 27% Grade I: 7% Grade II: 17% Grade III: 3%	99% (86/87)	8.1 ± 3.0 h (7.3 ± 1.9 h for desensitizations without BTR)
Sala-Cunill et al. 2021 (28) 1BP:109(434) 3BP:48(205)	Oxaliplatin:22 Carboplatin:50 Cisplatin:3 Paclitaxel:33 Docetaxel:6 Cetuximab:7 Rituximab:14 Other: 22	1BP-11S 3BP-10S	Initial HSR (Brown) for 1 BP and 3BP combined: Grade I: 56 (36%) Grade II: 67 (43%) Grade III: 34 (21%)	1BP BTR rate:49% Grade I: 40% Grade II: 7% Grade III: 2% 3BP BTR rate:48% Grade I: 31% Grade II: 17% Grade III: 0%	99.5(432/434) 99.5(204/205)	3.3-4.8 h. 4.3-5.8 h

Table I continue

Vetter et al. 2019 (32) 48(295)	Carboplatin: 36 Cisplatin: 12	1BP-4S 1BP-17S 3BP-16S	Initial HSR (*institutional) Moderate high-risk: 38 Severe: 10	1BP-4S: BTR rate: 65% ‡ 1BP-17S: BTR rate: 61%(severe: 0%)	97(285/295)	Carboplatin 4.3 h Cisplatin 5.3 h
Kim et al. 2022 (29) 228(1143)	Oxaliplatin:57 Carboplatin:49 Cisplatin:17 Paclitaxel:42 Docetaxel:12 Rituximab:37 Others:14	1BP-12S	24 completed ST: ST positive:14 ST negative:10 Initial HSR (Brown) Grade I: 11% Grade II: 57% Grade III: 32%	BTR rate: 26% No or grade I: 89% (all group) Grade III: 1% (platins) 4% (mAbs)	99	ND
Vazquez-Revuelta et al. 2023 (30) 65(263)	NR	1BP-10/16S	NR	No reaction: 79% Grade III: 2 patient	100	ND
Iglesias-Santamaría et al. 2023 (31) 17(130)	Carboplatin:12 Oxaliplatin:3 Paclitaxel:1 Brentuximab:1	1BP-16S	Initial HSRs (Brown) Grade I: 5 (29.4) Grade II: 5 (29.4) Grade III: 7 (41.2) 17 completed ST: Positive 15 (88.2) Negative 2 (11.8)	BTR rate: 23% Only grade I reaction with skin symptoms were observed in 23% (30/130) No grade II or grade III reaction	100	ND
Gül Ö et al. 2023 (33) 46(163)	Carboplatin:11 Oxaliplatin:14 Cisplatin:2 Docetaxel:8 Paclitaxel:8 Rituximab:2 Transtuzumab:1	1BP-12S	Initial HSRs (Brown) Grade I: 9 (19.6) Grade II: 26 (56.5) Grade III: 11 (23.9) 42 completed ST: Positive 15 Negative 27	BTR rate: 10.4% Grade I: 29.5% Grade II: 52.9% Grade III: 17.6%	99.3(162/163) §	ND

Rx: Reaction, **1BP:** One-bag protocol, **3BP:** Three-bag protocol, **S:** Step, **HSR:** Hypersensitivity reaction, **ST:** Skin test, **BTR:** Break-through reaction, **NR:** Not reported, **ND:** No data.

* Institutional classification: (1) mild: pruritus, facial flushing, localized rash, and drug fever less than 100.4°F; (2) moderate low-risk: diffuse erythema or urticaria, nausea/vomiting, abdominal pain, nasal congestion, dyspnea without hypoxia, coughing/wheezing, and drug fever of 100.4°F or greater; (3) moderate high-risk: transient (<10-min) signs or symptoms including hypotension or hypertension, tachycardia or bradycardia, chest pain, hypoxia, visual disturbance, tinnitus, and angioedema without anaphylaxis; (4) severe: sustained (_10-min) signs or symptoms including hypotension or hypertension, tachycardia or bradycardia, hypoxia despite oxygen supplementation, altered mental status, syncope and anaphylaxis.

† Institutional classification: (1) severe: at least one of the following: chest pain, dyspnea, oxygen desaturation, throat tightness, and blood pressure changes; (2) mild: none of the preceding.

‡ Two requiring epinephrine and one requiring hospitalization

§ One patient with a grade II BTR could not complete the RDD at the patient's own request.

Currently in a study conducted at our clinic, a total of 163 desensitization procedures were performed on 46 included patients, with 162 (99.3%) of them successfully completed. The rate of BTR was reported as 10.4%. Skin testing was performed on 91.3% of patients, making it one of the studies with the highest number of skin tests used as reported in the literature (33). Furthermore, although most studies with single bag desensitization protocol reported were with the platinum and taxane group chemotherapeutics or biological agents, there are also studies and case reports showing that the single-bag RDD procedure can also be applied for different drugs (27,28,34).

While the success rates are similar, differences in the inclusion criteria, patients' demographic characteristics, skin tests, and evaluation of reaction severity among the studies, as well as whether or not a drug provocation test was performed beforehand, and the different protocols applied, make it difficult to evaluate and compare outcomes of one-bag desensitization studies reported so far (30). Nevertheless, the importance of accurate risk assessments and prior skin tests for both drug provocation testing and decision-making in desensitization is increasingly emphasized with each study. This emphasis is also relevant for one-bag desensitization studies, with the adequacy of local resources being crucial in this regard (16,35,36).

One-bag desensitization studies have revealed some common results, despite differences in patient selection and evaluation of sensitivity and reactions before desensitization. The protocol has some advantages. Firstly, as previously mentioned, one-bag desensitization protocols are as safe and effective as multiple-bag desensitization protocols (24-33). Additionally, the stability of the drug is preserved with a single dilution solution (24). Secondly, one-bag RDD procedures eliminate the need for multiple dilutions and bag changes, thus reducing potential mistakes. Additionally, this protocol requires less effort from pharmacists and nurses, leading to savings in labor and costs. Timesaving is another advantage of one-bag RDD for both the patients and the healthcare system. While requiring less time, one-bag RDD can also provide outpatient treatment options, especially for patients without severe initial reactions (8,25,26).

CONCLUSION

While studies with chemotherapeutic agents and biological agents have proven the safety and efficacy of RDD application, the increasing interest in personalized medicine serves as motivation for new studies. New research should focus more on the risk factors, clinical phenotypes, and role of diagnostic tools for HSRs.

We have compiled the results of various clinical approaches by researchers for different patient groups who underwent one-bag RDD procedures. As seen, one-bag RDD protocols are as safe and effective as multiple-bag protocols in various patient populations. However, there is a need for a common strategy to classify patient groups to determine the most suitable RDD protocol and to compare one-bag studies with each other and with multiple-bag studies; broader studies are required to achieve this. It is undeniable that a multidisciplinary approach among allergy specialists, oncologists, and internal medicine specialists is necessary at this point.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authorship Contributions

Concept: **Ozcan Gul, Sevim Bavbek,** Design: **Ozcan Gul, Sevim Bavbek,** Data collection or processing: **Ozcan Gul, Sevim Bavbek,** Analysis or Interpretation: **Ozcan Gul, Sevim Bavbek,** Literature search: **Ozcan Gul, Sevim Bavbek,** Writing: **Ozcan Gul, Sevim Bavbek,** Approval: **Ozcan Gul, Sevim Bavbek.**

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