

One-Bag Desensitization Protocols in the Management of Chemotherapy Hypersensitivity



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Significant advances have been made in the field of evaluation and management of chemotherapy hypersensitivity reactions (HSRs) over the past 2 decades. Desensitization has been established as a safe and effective method for allowing patients with chemotherapy HSRs to continue first-line therapy. The most widely accepted protocols are multibag protocols in which serial 10-fold dilutions and stepwise increases in infusion rate allow incrementally increasing doses to be administered in a manner that promotes tolerance of the culprit chemotherapeutic agent.¹

Although effective, preparation and administration of multibag desensitization protocols can pose logistical challenges. Feasibility depends on available resources. In recent years, the advent of high-precision automatic pumps, which can infuse rates of 0.1 mL/h and enable delivery of minute drug doses previously achievable only by serial dilution, has led to the development of desensitization protocols that adhere to the incremental dosing principles of standard multibag protocols while requiring only one, undiluted bag. There is increasing interest in safety data and outcomes for these one-bag protocols (1BPs).

In this issue of *The Journal of Allergy and Clinical Immunology: In Practice*, Sala-Cunill et al² compare their experience with a 1BP for 109 patients undergoing 434 desensitizations between 2017 and 2019 to their experience with a three-bag, 10-step protocol for 48 patients undergoing 205 desensitizations between 2014 and 2016. The authors found no significant differences in the severity of breakthrough HSRs between the two protocols. Breakthrough HSRs decreased with repeated desensitizations for both protocols. Completion rates were high for both the 1BP (432 of 434; 99.5%) and three-bag protocol (3BP) (204 of 205; 99.5%) (Table I).

Their study is notable for reporting the largest number of patients receiving 1BPs to date, with a cohort consisting of relatively high-risk patients. Their protocol, along with most other previously published 1BPs ranging from four to 17 steps, differs in the number of steps and rates of administration from the standard 3BP with 12 or 13 steps (Table II).¹⁻⁸ These 1BPs

have been largely successful in allowing the completion of 97% to 100% of desensitizations with appropriate risk stratification (Table I). However, wide variability in baseline characteristics, including initial HSR severity and skin test positivity, the method used to grade HSR severity, criteria employed to assess risk for recurrent HSR, and the protocols themselves, limits the generalizability of the outcomes and the ability to draw large-scale conclusions from these studies.²⁻⁸

Their study is also notable for being the second publication to compare outcomes of a 1BP with a 3BP with near-equivalent number of steps at the same institution.^{2,6} This is important in a landscape where comparisons of 1BPs with 3BPs remain limited. A prior study by Lee et al⁶ found that the 1BP with 13 steps had similar, if not lower, breakthrough HSR compared with the 3BP with 12 steps. In the current study, distribution of the initial HSR severity was not compared between patients receiving 1BP versus 3BP, and severe breakthrough HSR occurred only with the 1BP, albeit in no more than two patients (2%). As such, it cannot be definitively concluded that the 1BP is truly noninferior to the 3BP in this study. However, their results are still promising for the expanding role of 1BPs in chemotherapy HSR management.

These comparison studies highlight a benefit of 1BPs over multibag protocols: time. Using a 1BP in lieu of a 3BP can save from 1 to over 5 hours, depending on the protocol and agent.^{2,6,8} In the current study, the 1BP required less time than the 3BP overall (195-290 vs 255-349 minutes), with a significant 154-minute reduction observed for the carboplatin 1BP and notable reductions observed for oxaliplatin (35-minute reduction), paclitaxel (48-minute reduction), and rituximab (45-minute reduction) 1BPs.

Given the documented shift toward outpatient desensitization at experienced centers,¹ the shorter duration of 1BPs as well as ease of preparation by pharmacists and administration by nurses may be particularly attractive to centers interested in transitioning desensitization to the outpatient setting. Inpatient admissions are resource-intensive, and outpatient desensitization can improve patient access and convenience. One study found that dedicated outpatient desensitization chairs led to a threefold documented reduction in mean time to start of desensitization.⁹ In addition, 1BPs using undiluted drug may address stability concerns for chemotherapy agents at dilutions employed in standard multibag protocols.¹⁰

Although 1BPs address a number of logistical concerns regarding multibag protocols, questions remain as to when it is medically appropriate to use 1BPs and whether the 1BP should be administered in an outpatient versus inpatient setting. Risk stratification is key to answering these questions. This study, along with prior publications on 1BPs, highlights the ever-important role of risk stratification in evaluating and

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TABLE I. Study cohorts and desensitization outcomes for previously published One-Bag Protocols

Publication	Agents (n patients)	Patient characteristics	1BP outcomes	3BP outcomes
Li et al (2014) ³ 1BP, four-step	18 patients Carboplatin: 13 Cisplatin: 5	Initial HSR (institutional*) • Mild: 9 (50%) • Moderate low-risk: 9 (50%)	95 desensitizations Breakthrough HSR: • Mild: 19% • Moderate: 12% • Severe: 1% Completed: • 99% (94 of 95)	NA
Perez-Rodriguez et al (2018) ⁴ 1BP, nine-step	90 patients Oxaliplatin: 30 Carboplatin: 16 Cisplatin: 3 Paclitaxel: 19 Docetaxel: 6 Cetuximab: 5 Rituximab: 6 Other: 8	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	490 desensitizations Breakthrough HSR: 5% (88% of platin desensitizations) • Grade I: 3% • Grade II: 2%† • Grade III: 0%† Completed • 99% (487 of 490)	NA
Sala-Cunill et al (2021) ² 1BP, 11-step 3BP, 10-step	1BP: 109 patients 3BP: 48 patients Oxaliplatin: 22 Carboplatin: 50 Cisplatin: 3 Paclitaxel: 33 Docetaxel: 6 Cetuximab: 7 Rituximab: 14 Other: 22	Grade III initial HSR (CTCAE version 5.0, Brown) Severe comorbidity -or- Positive ST Elevated tryptase -or- Positive drug provocation test Initial HSR (Brown) for 1 BP and 3BP combined: • Grade I: 56 (36%) • Grade II: 67 (43%) • Grade III: 34 (21%)	434 desensitizations Breakthrough HSR: 49% • Grade I: 40% • Grade II: 7% • Grade III: 2% Completed: • 99.5% (432 of 434) Duration: • 3.3-4.8 h	205 desensitizations Breakthrough HSR: 48% • Grade I: 31% • Grade II: 17% • Grade III: 0% Completed: • 99.5% (204 of 205) Duration: • 4.3-5.8 h
Chung et al (2018) ⁵ 1BP, 12- to 13-step	36 patients Oxaliplatin: 23 Carboplatin: 9 Cisplatin: 4	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	175 desensitizations Breakthrough HSR: 17% • Grade I: 9% • Grade II: 7% • Grade III: 1% Completed: • 100% Duration: • 3.9 h (4.2 ± 1.25 h including management of breakthrough HSRs)	NA

Lee et al (2020) ⁶ 1BP, 13-step 3BP, 12-step	1BP: 24 patients 3BP: 25 patients All paclitaxel	1BP initial HSR (Brown) • Grade I: 1 (4%) • Grade II: 14 (58%) • Grade III: 9 (38%) 3BP initial HSR (Brown) • Grade I: 1 (4%) • Grade II: 15 (60%) • Grade III: 9 (36%)	124 desensitizations Breakthrough HSR: 16% • Grade I: 7% • Grade II: 8% • Grade III: 1% Completed: • 98% (121 of 124) Duration: • 4.4 ± 2.5 h (4.1 ± 1.3 h for desensitizations without breakthrough HSR)	87 desensitizations Breakthrough HSR: 27% • Grade I: 7% • Grade II: 17% • Grade III: 3% Completed: • 99% (86 of 87) Duration: • 8.1 ± 3.0 h (7.3 ± 1.9 h for desensitizations without breakthrough HSR)
Vidal et al (2016) ⁷ 1BP, 16-step	12 patients Carboplatin: 8 Paclitaxel: 2 Docetaxel: 2	Initial HSR (institutional [†]) • Mild: 3 (25%) • Severe: 9 (75%) • ST-positive: 7 • ST-negative: 5	58 desensitizations Breakthrough HSR: • 0% [§] Completed: • 100%	NA
Vetter et al (2019) ⁸ 1BP, four-step 1BP, 17-step 3BP, 16-step	48 patients Carboplatin: 36 Cisplatin: 12	Initial HSR (institutional*) • Moderate high-risk: 38 (79%) • Severe: 10 (21%)	295 desensitizations Breakthrough HSR: • 1BP, four-step initially used but stopped owing to 65% patients experiencing breakthrough HSR (two requiring epinephrine and one requiring hospitalization) • 1BP, 17-step subsequently used with 61% patients experiencing breakthrough HSRs but 0% patients experiencing severe breakthrough HSR Completed: 97% • (285 of 295) Duration: • Carboplatin 4.3 h • Cisplatin 5.3 h	Five patients switched from 1BP, 17-step to 3BP owing to continued breakthrough HSR and completed subsequent desensitizations (exact number of desensitizations NR) Duration: • Carboplatin 9 h, cisplatin 14 h

1BP, one-bag protocol; 3BP, three-bag protocol; CTCAE, Common Terminology Criteria for Adverse Events; HSR, hypersensitivity reaction; NA, not available; NR, not reported; ST, skin test.

Study cohorts and desensitization outcomes are shown for publications reporting experiences with 1BPs. All 3BPs used serial 10-fold dilutions (1:100, 1:10, and 1:1).

*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.

[†]The authors reported that none of the breakthrough HSRs were grade III, but epinephrine was used for two of the grade II breakthrough HSRs.

[‡]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.

[§]One patient presented with mild pruritus during the third desensitization that resolved spontaneously in 10 minutes. Pruritus did not recur with subsequent 10 desensitizations.

TABLE II. Previously Published One-Bag Protocols

Publication	Li et al (2014) ³	Pérez-Rodríguez et al (2018) ⁴	Sala-Cunill and Molina-Molina et al (2021) ²	Chung et al (2018) ⁵	Lee et al (2020) ⁶	Vidal et al (2016) ⁷	Vetter et al (2019) ⁸
Concentration	Full strength, undiluted	Full strength, undiluted	Full strength, undiluted	Full strength, undiluted	Full strength, undiluted	1 mg/mL	Full strength, undiluted
Step 1	50	5	0.6	0.1	0.1	0.1-0.2	2
Step 2	150	10	1.2	0.2	0.2	0.2-0.3	4
Step 3	300	25	2.4	0.5	0.4	0.4-0.6	6
Step 4	600	50	4.8	1.2	0.8	0.9-1.2	8
Step 5		75	9.6	2.5	1.5	1.1-1.5	10
Step 6		100	19.2	5	3	2.2-3	15
Step 7		150	38.4	10	6	4.4-6	30
Step 8		200	76.8	20	12.5	8.8-12	60
Step 9		250	153.6	40	25	11-15	80
Step 10			307.2	60	50	22-30	100
Step 11			558	80	100	44-60	120
Step 12				150*	200	88-120	140
Step 13				450*	350	98-133	160
Step 14						195-267	180
Step 15						244-333§	200
Step 16						391-533§	400
Step 17							600
Duration, h	Carboplatin 1.5 Cisplatin 2.3	Depending on desired dose	3.3-4.8	3.9†	4.1 ± 1.3‡	4.5	Carboplatin 4.3 Cisplatin 5.3
Agents (total volume)	Carboplatin (500 mL) Cisplatin (1000 mL)	Oxaliplatin, carboplatin, cisplatin, paclitaxel, docetaxel, rituximab (500 mL) Cetuximab (250 mL)	Carboplatin (549 mL) Others not reported	Oxaliplatin, carboplatin (200 mL) Cisplatin (150 mL)	Paclitaxel (250 mL)	Rate and volumes adjusted to desired dose.	Carboplatin (500 mL) Cisplatin (1000 mL)
Location	Outpatient infusion center	Low- to medium-risk: outpatient oncology or allergy unit High-risk: intensive care unit	Low- to medium-risk: outpatient oncology day unit High-risk: intensive care unit	General inpatient wards	Not reported	Outpatient oncology day unit	Outpatient infusion center or outpatient acute care observation bed

Concentrations, rates (displayed as milliliter/hour), volumes, duration, and location are reported for previously published one-bag protocols.

*Final rate for carboplatin and oxaliplatin was capped at 150 mL/h versus 450 mL/h for cisplatin.

†Median actual time was 4.2 h (SD, 1.25 h) owing to additional time required to manage breakthrough hypersensitivity reactions.

‡Desensitization with breakthrough hypersensitivity reaction took 4.4 ± 2.5 h.

§These two steps were 30 min, as opposed to 15 min for other steps shown here.

managing chemotherapy HSRs. As such, when reviewing 1BP studies, it is important to note that (1) all except one of the 1BPs performed in the outpatient setting consisted of fewer steps than the standard 3BP with 12 steps, and (2) risk stratification was consistently employed to identify patients at lower risk for breakthrough HSR who could receive 1BPs as outpatients.^{2-4,8} In the two largest reports of 1BPs (including the study by Sala-Cunill et al²), only low- to medium-risk patients as determined by the investigators received outpatient 1BPs consisting of nine to 11 steps; high-risk patients were still admitted to the intensive care unit.^{2,4} Another institution created its own grading criteria to risk stratify mild and moderate/low-risk patients to outpatient 1BP with four steps (akin to a four-step graded challenge) and moderate- to high-risk patients to outpatient 1BP with 17 steps.^{3,8} Published 1BPs most similar to standard 3BPs were performed on general inpatient wards (the location is not reported in one study but was presumably inpatient, because both reports were from the same institution).^{5,6} Taken together, these findings suggest that published 1BPs may be safe to perform in the outpatient setting but require appropriate and careful risk stratification. Further study is needed to refine the criteria regarding when 1BP are safe, as well as when and if 1BP is safe to perform in the outpatient setting.

The authors add to the growing body of literature about undiluted 1BPs with one of the largest reports to date both in terms of number of patients and number of agents desensitized. Their findings support an expanding role for undiluted 1BPs in chemotherapy HSR management. Novel 1BPs show promise for facilitating outpatient desensitization because of the potential for simplified preparation and administration. Incorporating 1BPs safely into the standard care of chemotherapy HSR could improve patient access and convenience. To do this, clarification is needed as to whether 1BPs with 12 or 13 steps can be non-inferior to standard 3BP, in which case protocol selection would depend primarily on resource use. In addition, current literature suggests that outpatient 1BPs with fewer than 12 steps are most likely to be safe and effective for a subset of medium-risk patients who are too high-risk to receive a drug provocation test safely but are not high-risk enough to warrant inpatient desensitization.

Additional reports of clinical experiences are needed to confirm these findings and refine criteria for which patients can safely receive outpatient 1BPs with less than 12 steps. Continued investigation into the safety and outcomes of undiluted 1BPs will allow providers and institutions to incorporate these novel protocols into safe and personalized care of patients with chemotherapy HSR.

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