

Carboplatin Rechallenge After Hypersensitivity Reactions in Pediatric Patients With Low-Grade Glioma

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Background. The high prevalence of carboplatin hypersensitivity reactions (HSR) significantly affects the treatment of pediatric patients with low-grade glioma (LGG). Rechallenging patients is an option that must balance the risks of repeat allergic reaction to the benefits of retaining an effective anti-tumor regimen. **Procedure.** We performed a retrospective review of children with LGG treated with carboplatin and vincristine between October 2000 and April 2013, who had a documented HSR to carboplatin. Patients were re-exposed to carboplatin using either precautionary measures (prolonged infusion time and premedication with H1 antagonists, H2 antagonists, and

corticosteroids), a desensitization protocol, or both. **Results.** We report the results of our institutional experience of carboplatin re-exposure using both premedication with a prolonged infusion time and a desensitization protocol. Overall, 40 of 55 (73%) patients were successfully rechallenged with carboplatin, including 19 of 25 (76%) patients who underwent desensitization. **Conclusion.** Our results demonstrate re-exposure to be a safe alternative to abandoning carboplatin for patients with a hypersensitivity reaction. We propose a clinical algorithm for treatment. *Pediatr Blood Cancer* 2015; 9999:1–6 © 2015 Wiley Periodicals, Inc.

Key words: allergic reaction; carboplatin; desensitization; hypersensitivity; low-grade glioma; rechallenge

INTRODUCTION

Carboplatin, usually given with vincristine, is one of the front-line treatments for pediatric low-grade glioma (LGG).[1] The combination is associated with a 5-year event-free survival (EFS) of 39% in sporadic, and 69% in neurofibromatosis type 1 (NF1)-associated LGG.[2] Despite being relatively well-tolerated, hypersensitivity reactions (HSRs) to carboplatin are not infrequent (up to 40%).[3]

Other commonly used therapies for LGG include TPCV (thioguanine, procarbazine, lomustine, vincristine), vinblastine, bevacizumab/irinotecan, and temozolomide, as well as radiation therapy.[4–8] Each of these therapies has limitations, which include late toxicities such as second malignant neoplasms (TPCV, temozolomide, radiation), infertility (lomustine, procarbazine, bevacizumab), or vasculopathy/stroke (radiation), which can be more common in children with NF1, as well as concerns that the efficacy of these other options is no better than the first line regimen.[9–14] However, no randomized study (other than TPCV vs. carboplatin/vincristine) has been performed to directly compare these different regimens.[2] In order to avoid the risks or potential drawbacks of the other therapies, some have proposed desensitizing patients who have a carboplatin HSR, in order to continue a carboplatin-containing regimen.[15]

Here, we report our institutional experience rechallenging pediatric patients with LGG with carboplatin after a carboplatin HSR. Patients were re-exposed in two ways: using “precautionary measures” with premedication and a prolonged infusion time, or with a desensitization protocol. Our aim was to determine whether re-exposure to carboplatin is a viable option for continuing the carboplatin/vincristine regimen, and whether the desensitization protocol is a safe and effective option for patients who continue to have HSR despite precautionary measures.

METHODS

Study Population

This retrospective review was approved by the Children’s Hospital of Philadelphia (CHOP) institutional review board;

consent was waived. The study population consisted of children 0–18 years of age with LGG, who had a documented HSR to carboplatin. LGG was defined based on pathologic tissue biopsy in non-NF1 patients and based upon MRI appearance in those with NF1. All subjects were treated at The Children’s Hospital of Philadelphia and started chemotherapy (carboplatin and vincristine) no earlier than October 2000 and completed treatment by April 2013. Subjects were identified via a search of the electronic medical record (EMR) for carboplatin allergy and cross-referenced with a maintained list of patients who underwent carboplatin re-exposure or a desensitization protocol. Grading of the HSR was based on the common terminology criteria for adverse events (CTCAE) version 4.03.

Chemotherapy was given as per Arm A of CCG-9952[1] with an induction course (eight doses of carboplatin) and four courses of maintenance chemotherapy (two cycles per course with four doses of carboplatin each cycle) for a goal of a total of 40 doses of carboplatin. Patients with ongoing anti-tumor efficacy at the end of the planned maintenance course (reduction in tumor volume in the

Abbreviations: CHOP, Children’s Hospital of Philadelphia; CI, confidence interval; CTCAE, common terminology criteria for adverse events; EFS, event-free survival; EMR, electronic medical record; HSR, hypersensitivity reaction; KM, Kaplan–Meier; LGG, low-grade glioma; NF1, neurofibromatosis type 1; PICU, pediatric intensive care unit; TPCV, thioguanine, procarbazine, lomustine, vincristine; WHO, World Health Organization

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prior 6 months) often received additional cycles to optimize benefit from the therapy.

Treatment After HSR

The institutional clinical practice for most patients with a LGG and a carboplatin HSR was to attempt re-exposure using precautionary measures, which included prolonging the infusion time (from 1 to 2 hr); premedication with H1 antagonists, H2 antagonists, and corticosteroids; and escalated nursing monitoring in clinic. For patients with subsequent HSRs despite precautionary measures, or for those whose initial HSR was considered severe, carboplatin desensitization was considered. Premedications were included as part of the desensitization protocol. Each case was reviewed by the Neuro-oncology team and a collective decision made to pursue desensitization or not, based on potential risks (mainly of further or more severe HSRs), potential benefits (including continuing a treatment regimen with historical anti-tumor efficacy or that may be showing benefit in the patient currently), tumor response thus far, and a discussion with the family. Our desensitization protocol advanced carboplatin administration from an initial rate of 0.01 mg/min to a maximum of 1.5 mg/min over nine increments (Supplemental Table SI).

Five patients with repeat mild reactions occurring at high infusion rates on the standard desensitization protocol were treated with a modified version of the protocol in which the rate of drug administered never exceeded 0.5 mg/min. For nearly all patients undergoing desensitization, there was a minimum 2-week interval between HSR and starting desensitization. Initially, the first two carboplatin doses of the desensitization protocol were administered in the pediatric intensive care unit (PICU) for close observation, with subsequent doses administered in the oncology clinic. With experience, for later patients, all desensitization doses were administered in the clinic. Successful re-exposure to carboplatin was defined as the ability to complete the full planned course of treatment or to administer further doses as to provide clinical benefit (defined as a minimum of 1-year EFS from the end of therapy). All others for whom carboplatin was discontinued—due to either recurrent HSR or because of disease progression during rechallenge and the need to switch to salvage therapy—were considered a failure of re-exposure.

Statistical Analysis

Patient demographics were compared between the groups (precautionary measures only vs. desensitization) using χ^2 test for categorical variables such as gender and NF1 status and Wilcoxon test for continuous variables such as age. Rate of success of rechallenge was compared between the two groups using Fisher's exact test. In the desensitization group, rate of success of rechallenge was also compared between the patients who were desensitized immediately after their first HSR and those who were not, using Fisher's exact test. HSR timing was categorized as early (during induction or maintenance course #1) or late (course 2 or after). The success rate was compared between early versus late HSR, using Fisher's exact test. EFS is defined as time from initiation of therapy to the start of new therapy for recurrence, death, or the time of last follow-up. Kaplan–Meier (KM) method was used to estimate the EFS at various time points along with the 95% confidence intervals (CIs). Log-rank test was used to compare the EFS by the two groups of precautionary measures only versus desensitization, and also by the two groups of early HSR versus late HSR. A Cochran–Armitage Trend test was used to determine association between CTCAE grading of the initial HSR and ability to be successfully rechallenged with carboplatin. A two-sided *P*-value <0.05 is statistically significant.

RESULTS

Study Population

From October 2000 to April 2013, 144 pediatric patients with LGG were treated with carboplatin and vincristine. Of these, 56 patients (38.9%) experienced a hypersensitivity reaction to carboplatin. One patient was immediately switched to an alternate therapy because neuro-ophthalmologic examination demonstrated worsening vision. The other 55 patients were re-exposed to carboplatin initially using either precautionary measures (49 patients) or immediately with a desensitization protocol (six subjects). Of the 49 patients who initially received post-HSR carboplatin with precautionary measures, 19 were later switched to a desensitization protocol (bringing the total desensitized to 25). There were no significant differences in gender, NF1 status, median age at treatment initiation, or tumor location between the 30 patients who were re-exposed to carboplatin using precautionary measures alone (the “nondesensitized patients”) compared to the 25 patients

TABLE I. Patient Characteristics

Characteristic	Total (N = 55)	Non-desensitized (N = 30)	Desensitized (N = 25)	<i>P</i> -value
Male (%)	28 (51)	17 (56.7)	11 (44)	0.422
Neurofibromatosis type 1 (%)	26 (47.3)	14 (46.6)	12 (48)	0.921
Age in years at therapy start, median (range)	3.1 (0.4–15.2)	3.3 (0.5–15.2)	3 (0.4–9.3)	0.440
Tumor location (%)				0.228
Optic pathway/hypothalamic	39 (70.9)	20 (66.6)	19 (76)	
Other diencephalon	3 (5.5)	2 (6.7)	1 (4)	
Cerebral hemisphere	3 (5.5)	1 (3.3)	2 (8)	
Cerebellum	3 (5.5)	2 (6.7)	1 (4)	
Brainstem	4 (7.3)	2 (6.7)	2 (8)	
Spine	2 (3.6)	2 (6.7)		
Multiple locations	1 (1.8)	1 (3.3)		

who underwent a desensitization protocol (the “desensitized patients”) (Table I).

Factors in Deciding Treatment

The decision to rechallenge a patient using a desensitization protocol was based on five major factors. Eighty percent of the 25 desensitized subjects were continued on carboplatin primarily because of documented disease response (16 patients with decreased tumor size or stabilization of previously growing tumor), and/or improvement in vision or stabilization of previously declining vision ($n=4$) from the chemotherapy prior to their hypersensitivity reaction. Two patients were referred for desensitization because of improvement in neurologic function (regaining previously lost developmental milestones) after starting carboplatin. For two patients (neither of whom had NF1), the major deciding factor was the families’ preference to specifically avoid TPCV as an alternate regimen because of the relative increased risk of secondary malignancy. For one patient, the HSR occurred so early in therapy, it was felt to be premature to abandon carboplatin.

Although five major factors were repeatedly documented as the primary reason for choosing a desensitization protocol, we speculated that both timing of the first HSR and CTCAE grading of the HSRs contributed to the decision to desensitize. Most patients (62%) had their first HSR early (induction or maintenance course #1) with 87% occurring prior to the end of maintenance course #2 (Fig. 1). We found no bias in choosing a particular method of rechallenge (precautionary measures versus desensitization) based on the timing of the first HSR. Patients who were begun immediately on a desensitization protocol after an initial HSR had their first HSR at a median of 16 doses of carboplatin versus a median of 14 doses for those who attempted precautionary measures first.

The CTCAE grade of the first reaction did not appear to play a role in deciding to abandon carboplatin. Only one patient discontinued carboplatin after first HSR without attempting re-exposure, and this was due to a concomitant finding of worsening vision despite chemotherapy. The HSR grade, however, did seem to contribute to the decision to first trial precautionary measures or to

proceed immediately to desensitization. The first HSR was high-grade (III or IV) in 14 patients; of these, six (43%) moved to desensitization immediately, including the only two patients with initial grade IV HSR. In contrast, no patients (out of 41) moved immediately to desensitization without first attempting precautionary measures if their first HSR was low-grade (I or II). Fourteen of these 41 (34%) eventually experienced grade III or IV HSR with subsequent doses, at which time they were switched to desensitization (Table II).

Outcome

In our cohort, 40 of 55 patients (73%) were successfully rechallenged with carboplatin. Of these 40 patients, 34 completed the full planned course of therapy. Despite stopping therapy early, the other six patients were able to receive multiple additional doses of carboplatin (10, 10, 13, 15, 15, and 28 doses) and were progression-free for at least a year after ending therapy. There was no difference in success of carboplatin rechallenge between the patients who received precautionary measures only (21 of 30, or 70% successfully rechallenged) compared to those who underwent a desensitization protocol (19 of 25, or 76% successfully rechallenged) ($P=0.764$). Of the 49 subjects who were initially rechallenged with carboplatin using precautionary measures, 21 (43%) were successfully re-exposed using this alone (Fig. 2). Another 19 were switched from precautionary measures to desensitization, 16 of whom were successfully re-exposed (84%), thereby rescuing the majority of patients for whom precautionary measures were insufficient. The majority (12 of the 19 patients), who first attempted precautionary measures and then switched to desensitization (in gray, Fig. 1), switched after four or fewer doses. For all subjects, a median of 22 (range 1–67) subsequent doses of carboplatin were successfully administered after an initial carboplatin HSR.

Of the 15 subjects who failed carboplatin rechallenge, nine subjects discontinued carboplatin because of either recurrent same-grade HSR ($n=2$) or because of progression to a higher grade HSR ($n=7$). Six subjects were safely administered further carboplatin doses (ranging from 15 to 21) but were eventually switched to an

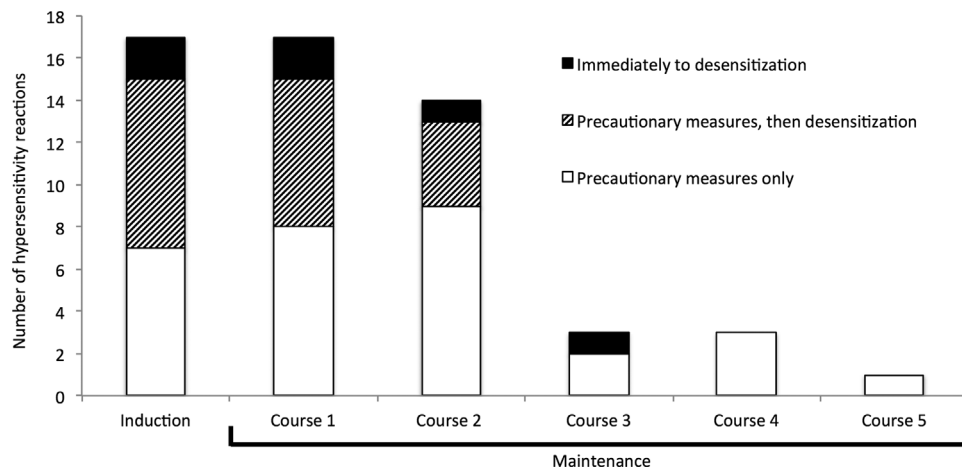


Fig. 1. Timing of first HSR differentiated by whether further carboplatin doses were administered by precautionary measures alone (white), desensitization alone (black), or both (gray). Maintenance course 5 refers to one subject who was treated beyond the planned four courses (eight cycles) of maintenance therapy.

TABLE II. Subsequent High-Grade HSRs Occurring After Initiating Carboplatin Rechallenge

Grade of initial HSR	Total (55)	Patients experiencing a subsequent high-grade HSR (Grade III or IV)			
		Patients rechallenged by precautionary measures alone	Patients rechallenged by desensitization after failing precautionary measures	Patients rechallenged by desensitization alone	All rechallenged patients
Grade I	14	2/9 (22%)	4/5 (80%)	–	6/14 (43%)
Grade II	27	2/13 (15.4%)	6/14 (43%)	–	8/27 (30%)
Grade III	12	4/8 (50%)	–	1/4 (25%)	5/12 (42%)
Grade IV	2	–	–	0/2 (0%)	0/2 (0%)

HSR, hypersensitivity reaction.

alternate chemotherapy regimen because of tumor progression. Importantly, none of our subjects required hospitalization as a result of an HSR during carboplatin rechallenge.

The 5-year EFS for our cohort of 55 patients who underwent carboplatin rechallenge after an HSR is 77.1% (95%CI 57.7–88.5%). There was no difference in the success rate of re-exposure ($P = 0.282$) or EFS ($P = 0.888$) when comparing patients with an early HSR (during induction or maintenance course 1; HSR occurring at a median dose of 7) compared to those who had later HSRs (during course 2 or after; median dose = 15.5). Among the patients who were desensitized, there was no difference in success of re-challenge between patients who were desensitized immediately after their first HSR relative to those who began desensitization after receiving multiple additional carboplatin doses with precautionary measures alone ($P = 0.087$).

We examined whether the grade of the initial HSR affected the success of rechallenge (Table III). Nearly all patients with an initial Grade I HSR were successfully rechallenged (93%), despite the fact that a majority (85%) at some point progressed to a higher HSR event during rechallenge (five progressed to Grade II, six to Grade III, none to Grade IV). Patients with an initial Grade II HSR also did well overall (74% completed therapy), with patients performing slightly but not significantly better with desensitization (79% success rate) over precautionary measures alone (69%). In contrast, those with an initial Grade III HSR had the worst success rate, regardless of the rechallenge method. Conversely, the desensitization protocol was successful in rechallenging both patients with an initial Grade IV HSR. In summary, 19 patients had no further HSRs after their initial reaction, 12 had repeat HSRs of the same ($n = 8$) or

lesser CTCAE grade ($n = 4$), and 24 had subsequent HSRs of more severe grade.

When evaluated based on the highest grade HSR experienced, patients with a Grade III or IV HSR were significantly less likely to be successfully rechallenged than those with a Grade I or II HSR ($P = 0.036$). The majority of these failed rechallenges were in those who received only precautionary measures. Of patients with highest HSR grade (III or IV), only 5 of 12 (41.6%) successfully completed therapy using precautionary measures alone, whereas 14 of 17 patients (82.5%) successfully completed therapy when desensitization was used.

There were no significant differences between patients with NF1 and those without NF1 with respect to initial HSR grade ($P = 0.529$), success rate of rechallenge (84.6% for NF1, 62.1% for non-NF1 patients; $P = 0.076$), or 5-year EFS (NF1: 71.4%, 95% CI 44.3–87.0%; non-NF1: 85.6%, 95%CI 53.3–96.2%; $P = 0.306$).

DISCUSSION

The results from this retrospective study demonstrate the efficacy of both precautionary measures and a desensitization protocol for continued treatment with carboplatin after an HSR. This is the largest reported group of patients with a carboplatin HSR who have been re-exposed to the drug. Our carboplatin HSR incidence is similar to prior studies, which report a rate up to 40% of those exposed to carboplatin.[15–16] In contrast to other studies suggesting an increased risk of HSR in female patients, our cohort did not demonstrate this risk of HSR, nor differential benefit from carboplatin re-exposure.[17] Overall, we noted 73% of patients were successfully re-exposed to carboplatin, 16% failed the rechallenge, and the remaining 11% were not continued on a rechallenge protocol due to disease progression. This success rate was noted despite this study's definition for failure, which included patients who could not continue rechallenge with carboplatin due to tumor progression. Of the 49 patients rechallenged with precautionary measures, 21 (43%) completed carboplatin therapy with precautionary measures only. Additional 16 patients (out of 19 who were switched to desensitization) were able to be rescued with the desensitization protocol after having subsequent significant HSRs when rechallenged with precautionary measures.

Our patient cohort did not demonstrate an inferior time to progression, whether rechallenged with precautionary measures alone or desensitization, compared to historical controls, supporting the rationale for these re-exposure approaches.[2] In addition, our results support the safety of re-exposure after a carboplatin HSR.

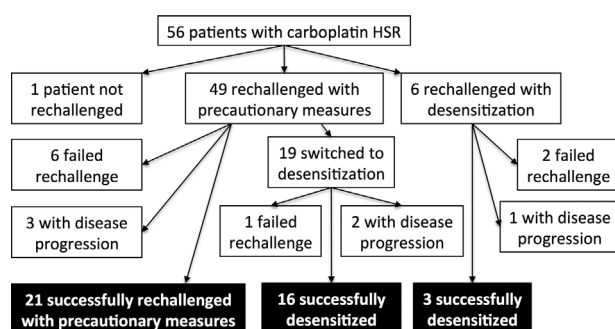


Fig. 2. Breakdown of therapy given after carboplatin hypersensitivity reactions.

TABLE III. Outcome of Patients Based on Grade of Initial HSR

Grade of initial HSR	Total (55)	# Successful by precautionary measures (%)	# Successful by desensitization (either upfront or switched from precautionary measures) (%)	Overall percent successful (%)
Grade I	14	8/9 (89)	5/5 (100)	93
Grade II	27	9/13 (69)	11/14 (79)	74
Grade III	12	4/8 (50)	1/4 (25)	42
Grade IV	2	–	2/2 (100)	100

HSR, hypersensitivity reaction.

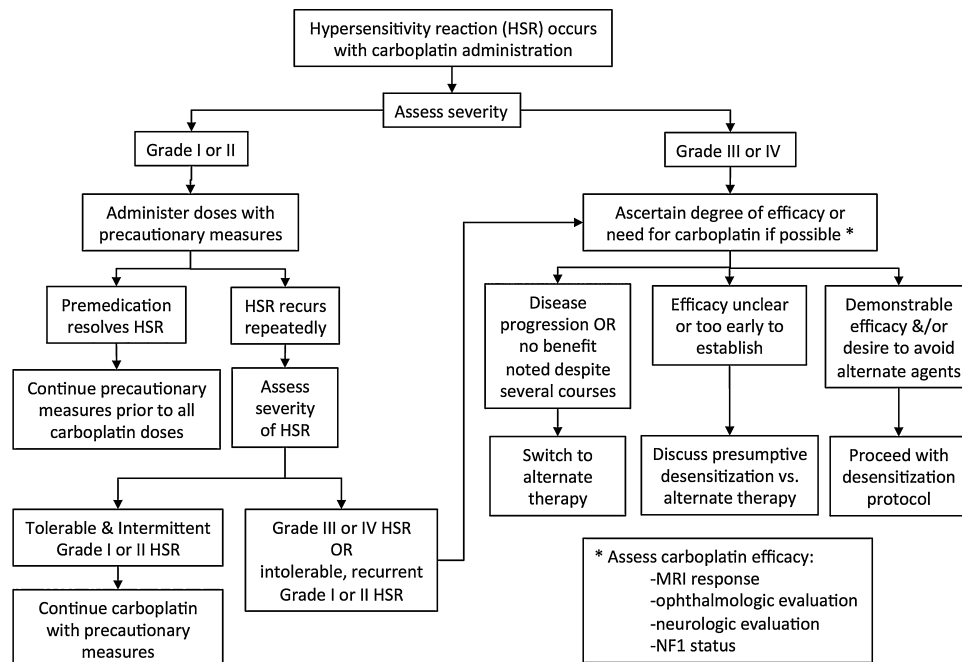
No patients who had a Grade III or IV reaction completed therapy with precautionary measures only; in all cases, carboplatin was either abandoned or a desensitization protocol initiated. In our cohort, all patients who developed a Grade IV reaction while being rechallenged with precautionary measures abandoned carboplatin therapy; however, all three subjects rechallenged with desensitization despite a Grade IV HSR were successfully treated. This included two patients whose initial HSR was Grade IV and a third patient developed a Grade IV reaction during desensitization. Although in our cohort, all three patients with a Grade IV HSR successfully completed therapy, the risks of and need for rechallenge must be carefully considered before continuing carboplatin. If rechallenge is considered necessary, we recommend moving straight to desensitization.

Our experience is similar to other reports of successful desensitization in adults with carboplatin HSRs.[18,19] In contrast, prior pediatric studies suggest that the rate of successful desensitization was not high enough to warrant the practice.[17] There may have been differences in the protocols for re-exposure to carboplatin that explain the higher success rate of our institutional experience compared with other reports. Our precautionary measures incorporated not only premedications but also increased

infusion time to 2 hr. In addition, our desensitization protocol was administered in a slow step-wise fashion with limits on the rate of infusion and was consistently nearly 6 hr in length, instead of varying between 1 and 6 hr.[17] It is possible that greater consistency in utilizing a prolonged infusion time and limiting the highest infusion rate resulted in improved efficacy of our desensitization protocol and explain the differences in our results.

It has been argued that rigorous protocols of desensitization often involve critical care unit availability and prolonged administration schedules that can be cost- and time-intensive as well as anxiety-inducing and burdensome to the patient, family, and caregivers.[18] We agree and suggest that it is important to ensure patient families understand both the immediate risk of more severe HSRs and the potential long-term consequences of repeated steroid utilization as a premedication. In addition, they must weigh quality of life and cost of issues such as prolonged clinic visits for desensitization with the outcomes associated with other therapies and the risks of those therapies to make an informed decision.

Given our results, we propose the following algorithm to help guide decision making in cases of a carboplatin HSR, taking into account the grade of HSR, effectiveness of therapy prior to HSR, and NF1 status (Fig. 3). Although MR imaging will be the most


Fig. 3. Algorithm for carboplatin re-exposure in pediatric patients with low-grade glioma experiencing a carboplatin HSR.

common method of assessing the efficacy of the regimen and will help determine the risks and benefits of rechallenge, functional outcomes such as changes in vision or neurologic function may also guide the decision. A patient's NF1 status, and thus increased risk of secondary malignancy with alternate chemotherapeutic regimens, should also be considered. In addition, timing of HSR should be taken into account, given that those with HSR occurring earlier in the course of treatment may be at slightly higher risk of failing rechallenge. Some of these patients may benefit by going directly to desensitization over using precautionary measures alone.

In most cases of Grade I or II HSR, if disease has not progressed, re-exposure to carboplatin is a valid option, starting with precautionary measures, given its success rate following low-grade HSR and the time commitment of desensitization. For high-grade HSR, our results suggest utilizing desensitization. For Grade III HSR, there is an overall higher success rate when using desensitization (79%) versus precautionary measures alone (42%). The poor success rate of those with an initial Grade III may be a reflection that 75% of them were rechallenged with precautionary measures alone. Although small numbers, those with a Grade IV HSR were able to successfully complete therapy and none had repeat reactions requiring hospitalization. Finally, the desensitization protocol would also be available for patients who fail administration of repeat doses of carboplatin with precautionary measures alone. Considering the high number of patients who seem to exhibit carboplatin HSR and the limited efficacy of other treatment regimens, we recommend consideration of this algorithm for both NF1 and non-NF1 patients.

There are several points to consider when implementing this algorithm. Every patient who received "precautionary measures" prior to and during rechallenge with carboplatin received premedication with corticosteroids and H1 and H2 antagonists, and had carboplatin infused over a prolonged time (2 hr) with escalated nurse monitoring. We are unable to evaluate the efficacy of using fewer measures, but would hesitate to use less when rechallenging a patient after an HSR. Second, we initially performed the first two doses of desensitization for patients in the pediatric ICU, and then with experience transitioned to administering the desensitization protocol completely in our oncology clinic with close observation. In fact, for those desensitized, only three advanced from a lower to higher grade HSR and they all did so within the first few doses. In contrast, nine patients re-exposed with precautionary measures experienced higher grade HSRs, seven within the first one to two doses of re-exposure. This suggests that the patients undergoing simple re-exposure with precautionary measures are more likely to have subsequent severe reactions and require a higher level of

observation. Overall, the decision to rechallenge in the clinic versus the ICU is an institution-dependent determination based on staffing and level of support available in the clinic, as well as the experience of the physician and clinic staff and the availability of a rapid response team in the event of an emergency. Last, of our small number of patients who received the modified desensitization protocol (with an infusion rate not exceeding 0.5 mg/min), only one of the five failed rechallenge with an HSR. Thus, for those with continued reactions at the higher infusion rates on the standard desensitization protocol, it may be effective to use this type of modification.

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Supplemental Table 1. Typical desensitization protocol with cumulative carboplatin dose to be administered based on subject body surface area.

Dose #	Rate (mg/min)	Concentration	Administration
1 st	0.01	0.01 mg/mL	IV over 1 min, 60mL/hr, then 14 min break
2 nd	0.1	0.1 mg/mL	IV over 1 min, 60mL/hr, then 14 min break
3 rd	0.5	0.5 mg/mL	IV over 1 min, 60mL/hr, then 14 min break
4 th	1	0.5 mg/mL	IV over 1 min, 120mL/hr, then 14 min break
5 th	1	0.5 mg/mL	IV over 2.5 min, 120mL/hr, then 12.5 min break
6 th	1	0.5 mg/mL	IV over 5 min, 120mL/hr, then 10 min break
7 th	1	0.5 mg/mL	IV over 10 min, 120mL/hr, then 5 min break
8 th	1.5	0.5 mg/mL	IV over 10 min, 180mL/hr, then 15 min break
9 th	1.5	0.5 mg/mL	180mL/hr until finished, then 45 min observation