

# Desensitization to carboplatin in low-grade glioma. A revision of 100 treatments in children

To the Editor,

Hypersensitivity reactions (HSR) in children during chemotherapy have been increasingly documented.<sup>1</sup>

Rapid drug desensitization (RDD) is practically unknown to most oncologists despite allowing patients to be treated with first-line agents. In pediatric age, there is a lack of guidelines and general principles have been adapted from adults (Figure 1).

Carboplatin is used for the treatment of a wide range of tumors, and the combination with vincristine is the most widely adopted scheme for childhood low-grade glioma (LGG).<sup>2</sup>

The aim of this letter is to report a 10-year period of experience with RDD to carboplatin in children diagnosed with LGG in a tertiary hospital.

Clinical records of children submitted to RDD to carboplatin between July 2009 and April 2019 were reviewed.

Skin prick tests (10 mg/mL) and intradermal tests (1 and 10 mg/mL) with carboplatin were performed according to international recommendations.<sup>3</sup> To minimize pain, a prilocaine-lidocaine patch (EMLA®) was applied 30–60 minutes before.

In all cases, the decision to proceed to RDD was based on a strong clinical suspicion of HSR plus the absence of an equally safe and effective alternative treatment.

In all cases, the family was informed about the risk-benefits of this procedure. Motivation and ability to collaborate were assessed. It should be noted that in no case, the lack of family support restrained the protocol; hospital settings and therapeutic schedule were adapted in case of family limitations.

All patients were desensitized under close supervision of allergists. In milder cases, RDDs were performed in the pediatric oncology day hospital/pediatric ward. In cases of anaphylaxis, the first RDD was performed in the intensive care unit. In the absence of breakthrough reactions (BR), subsequent treatments were moved to usual facilities.

Until 2011, an adapted Cofino-Cohen protocol was applied;<sup>4</sup> subsequently, the protocol developed by Castells<sup>3</sup> was used.

Protocols were designed according to the intended cumulative dose and severity of the IR ("tailor-made"). A 12-step protocol with 3 parental preparations with progressive concentrations at incremental rates was initially performed. The usual protocol included pre-medication with antihistamine and methylprednisolone (1 mg/kg) 1 hour before the infusion, intravenous hydration, and ondansetron.

If needed, adaptations of the initial protocol, including the addition of several intermediate steps and even of a fourth bag, were performed as well as a pre-medication reinforcement.

A total of 48 patients received intravenous carboplatin for LGG, and 15 had a reaction compatible with an IgE-mediated HSR (incidence of 31%).

All were being treated with carboplatin (550 mg/m<sup>2</sup>) plus vincristine. The median age at the IR was 3 years old (range, 18 months–9 years old) (Table 1). A median of 8 cycles of carboplatin was performed until the IR, the majority starting <30 minutes after infusion (all within 1h). The clinical pattern varied from moderate (isolated mucocutaneous symptoms in 6 cases) to severe (9 anaphylactic reactions). Acute and baseline tryptase was measured in only 5 of 9 patients with anaphylaxis and was elevated (baseline tryptase  $\times$  1.2 + 2 ng/mL) in 3. Only one patient received epinephrine.

Skin tests (ST) were negative in the 4 tested patients.

No schedule delays due to desensitizations procedures occurred.

In total, 100 RDDs to carboplatin were performed with a median of 6.7 treatments per patient. In 6 patients, RDDs were successful in the first treatment, and in 9 patients (60%), adaptations to the initial protocol and reinforcement of pre-medication were performed (antihistamines, corticosteroids, and montelukast). The BR were more severe than the initial reaction in 4 patients.

In the majority of cases (78%), BR were successfully managed by discontinuing the infusion and administering rescue medication; the infusion was only restarted once the symptoms resolved.

In 2 patients, the RDDs were unsuccessful due to severe BR despite adaptations and an alternative drug was used.

## DISCUSSION

Literature data on carboplatin HSR in children with LGG are limited. The higher rate of HSR was found in the cohort of Dudgshun et al<sup>5</sup> and the frequency differed according to the protocol used; 8% of patients treated with only carboplatin and 68% of those with combined carboplatin and vincristine presented HSR, respectively. An immune potentiating effect of the association of the drugs was hypothesized. In our study, all patients were treated with carboplatin and vincristine but our rate of HSR was significantly lower. Our study did not

## Main protocol for 407 mg carboplatin desensitization

Solution	Total Volume	Concentration	Dose
Solution A	250 mL	0.02 mg/mL	5 mg
Solution B	250 mL	0.2 mg/mL	50 mg
Solution C	250 mL	2 mg/mL	500 mg

Step	Solution	Rate (ml/h)	Time (min)	Volume (mL)	Dose (mg)	Cumulative Dose (mg)
1	A	2	15	0.5	0.01	0.01
2	A	5	15	1.25	0.025	0.035
3	A	10	15	2.5	0.05	0.085
4	A	20	15	5	0.1	0.185
5	B	5	15	1.25	0.25	0.435
6	B	10	15	2.5	0.5	0.935
7	B	20	15	5	1	1.935
8	B	40	15	10	2	3.935
9	C	10	15	2.5	5	8.935
10	C	20	15	5	10	18.935
11	C	40	15	10	20	38.935
12	C	80	145	193.5	387	407

**Scenario 1.** Recurrent generalized urticaria at the 9<sup>th</sup> step requiring antihistamines and corticosteroids.

An additional step was added

Solution	Total Volume	Concentration	Dose
Solution A	250 mL	0.02 mg/mL	5 mg
Solution B	250 mL	0.2 mg/mL	50 mg
Solution C	250 mL	2 mg/mL	500 mg

Step	Solution	Rate (ml/h)	Time (min)	Volume (mL)	Dose (mg)	Cumulative Dose (mg)
1	A	2	15	0.5	0.01	0.01
2	A	5	15	1.25	0.025	0.035
3	A	10	15	2.5	0.05	0.085
4	A	20	15	5	0.1	0.185
5	B	5	15	1.25	0.25	0.435
6	B	10	15	2.5	0.5	0.935
7	B	20	15	5	1	1.935
8	B	40	15	10	2	3.935
9	C	5	15	1.25	2.5	6.435
10	C	10	15	2.5	5	11.435
11	C	20	15	5	10	21.435
12	C	40	15	10	20	41.435
13	C	80	137	182.8	365.6	407

**Scenario 2.** Anaphylaxis at the 3<sup>rd</sup> step. An additional bag was added.

Solution	Total Volume	Concentration	Dose
Solution A	250 mL	0.002 mg/mL	0.5 mg
Solution B	250 mL	0.02 mg/mL	5 mg
Solution C	250 mL	0.2 mg/mL	50 mg
Solution D	250 mL	2 mg/mL	500 mg

Step	Solution	Rate (ml/h)	Time (min)	Volume (mL)	Dose (mg)	Cumulative Dose (mg)
1	A	2	15	0.5	0.001	0.001
2	A	5	15	1.25	0.0025	0.0035
3	A	10	15	2.5	0.005	0.0085
4	A	20	15	5	0.01	0.0185
5	B	5	15	1.25	0.025	0.0435
6	B	10	15	2.5	0.05	0.0935
7	B	20	15	5	0.1	0.1935
8	B	40	15	10	0.2	0.3935
9	C	10	15	2.5	0.5	0.8935
10	C	20	15	5	1	1.8935
11	C	40	15	10	2	3.8935
12	C	80	15	20	4	7.8935
13	D	20	15	5	10	17.8935
14	D	40	15	10	20	37.8935
15	D	80	15	20	40	77.8935
16	D	100	99	164.6	329.1	407

**FIGURE 1** For understanding purpose, an adapted protocol was adjusted according to 2 hypothetical scenarios, based on our patients

include patients that tolerated subsequent infusions after preventive measures were started, and this may explain the results' difference as only one-third of *Dodgshun's* patients were desensitized with carboplatin.

In accordance with previous studies, the reactions begun at the eighth cycle; the risk of hypersensitivity to carboplatin seems to be related to the cumulative number of exposures rather than to the cumulative dose itself.<sup>1,3,6,7</sup>

Anaphylaxis represented 60% of the IR, in agreement with the literature which reports that most of platinum HSR are severe.<sup>8</sup>

Only one patient was treated with adrenaline, which emphasizes the worldwide reality in which anaphylaxis is often under recognized and under-treated.<sup>9</sup>

ST to carboplatin have been recommended between the fifth and eighth cycle in order to predict the risk of future HSR.<sup>10</sup> However, the implications of a positive test are not clear, especially in children. The young age and the fragility of these patients also justified skipping this prophylactic ST in our children.

Diagnostic ST to carboplatin were not performed in every patient as the optimal timing could imply a treatment delay. Of the 4 patients tested, none had positive ST. Non-irritative concentrations are only validated in adults and children may behave differently and display positive results less frequently or with different concentrations.<sup>11</sup> Validation of ST with EMLA® with other drugs found no differences in ST results but platins were not evaluated in this study.<sup>12</sup>

TABLE 1 Characteristics of children that underwent rapid drug desensitisation with carboplatin

P	Gender	Age at IR	No of cycle	IR Characteristics	IR Grade	Protocol, target dose (mg)	No of DP	Description of DZT-related adverse events	Protocol adaptation	Protocol suspension
1	F	3	U	Lip and orbital Ao and paresthesia of the feet	Mild	Confino-Cohen, 354	2	Lip Ao	No	No
2	M	9	8	Lip Ao, plantar itch, dysphagia, and dyspnea	Moderate	Confino-Cohen, 700	4	Generalized erythema, lip Ao, odynophagia, nasal pruritus, stridor, and abdominal pain	Yes	No
3	M	7	10	Lip Ao, facial flushing, and dysphonia	Moderate	Confino-Cohen, 440	14	Absent	No	No
4	F	3	7	Facial Ao and generalized erythema	Mild	Confino-Cohen, 467	8	Facial flushing and lip Ao	No	No
5	F	3	8	Generalized erythema and orbital Ao	Mild	Castells, 473	4	Ao and flush of the face and desaturation with labial cyanosis	Yes	No
6	M	2	6	Generalized erythema	Mild	Castells, 500	9	Absent	No	No
7	M	9	8	Face and trunk erythema, sneezing, cough, dyspnea, and abdominal pain	Moderate	Castells, 706	6	Generalized erythema and tachypnea	No	No
8	F	7	10	Generalized erythema, ocular congestion, cough, dyspnea, stridor, desaturation with labial cyanosis, and vomiting	Severe	Castells, 500	6	Generalized pruritus, facial Ao, and abdominal pain	Yes	No
9	M	3	7	Generalized erythema and orbital Ao	Mil	Castells, 346	3	Generalized erythema, palmoplantar pruritus, odynophagia, and abdominal pain	Yes	Yes
10	F	3	8	Generalized erythema	Moderate	Castells, 435	6	Nose and ear redness and fever	No	No
11	F	1	9	Facial and trunk erythema and fever	Moderate	Castells, 279	3	U	Yes	Yes
12	F	4	10	Facial and trunk maculopapular exanthema and cough	Moderate	Castells, 374	6	Face erythema, orbital Ao, and crying hoarseness	Yes	No
13	M	2	6	Face erythema and Ao oropharyngeal pruritus and cough	Moderate	Castells, 550	11	Generalized erythema and nausea	No	No
14	M	4	8	Face erythema, ear Ao, odynophagia, cough, bronchospasm, stridor, and desaturation with labial cyanosis	Severe	Castells, 396	11	Generalized erythema, cough, bronchospasm, vomiting, and prostration	Yes	No
15	F	4	2	Face and trunk maculopapular exanthema	Mild	Castells, 327	7	Generalized pruritic exanthema	Yes	No

Note: Only patient 3 had been previously exposed to the drug 5 years earlier, as the HSR occurred during a new treatment after disease progression. Patients 6, 7, 12, and 14 were atopic. Only patient 2 was treated with epinephrine at the IR. Skin tests were performed in patients 1, 2, 3, and 5. Only patient 5 had positive intradermal test. Specific IgE to carboplatin and to cisplatin was evaluated in patients 2, 3, and 5 and was positive only in patient 5 (carboplatin: 1.6 kU/L and cisplatin: 4.2 kU/L, UniCAP; Pharmacia, Uppsala, Sweden). Severity of reactions was classified according to the adapted Brown criteria.<sup>1</sup> After carboplatin discontinuation, vinblastine was prescribed in patient 11 and cyclophosphamide in patient 9.

Abbreviations: Ao, Angioedema; DP, desensitization procedures; F, female; IR, initial reaction; M, male; MC, mucocutaneous; P, patient; U, unknown.

Although none of the suspected HSR was confirmed by ST, the high rate of BR during RDD (60%) corroborates the initial diagnosis.

Only 2 patients (13%) failed RDD. They had bothersome symptoms that persisted or even worsened with RDD despite several modifications to the initial protocol.

BR during RDD were more severe than the IR in 4 cases; a more accurate characterization of the reactions by allergists might be an explanation.

The success rate of RDD to carboplatin in this study was 87%, comparable to rates<sup>3</sup> in adult series, but significantly different from some of pediatric series with higher success rates observed in milder reactions or lower carboplatin doses.<sup>1,5-7,11</sup>

The SIOP guidelines<sup>2</sup> discourages RDD to carboplatin; nevertheless, RDD has been successfully performed in our department as in several other centers.<sup>4,6,7,11</sup> However, the high rate of severe reactions during RDD highlights the importance of such procedures to take place under the supervision of an allergist, in a pediatric oncology center.

RDD was performed even in infants that achieved several years of survival after treatment. Two patients (4 and 5) died after treatment conclusion due to disease progression.

Limitations of the study include the small number of patients and the absence of all data in some patients due to its retrospective nature.

In conclusion, clinicians must not underestimate the potential risk of HSR to chemotherapy in children. However, RDDs performed under suitable conditions can be an option for these patients, improving the final oncologic outcome. To our knowledge, this is the biggest case series on desensitization to carboplatin in children.

## CONFLICT OF INTEREST


The authors declare no conflicts of interest.

## AUTHOR CONTRIBUTIONS

**Leonor Carneiro-Leão:** Visualization (equal); Writing-review & editing (equal).

## ETHICAL STATEMENT

The study conforms to the ethical principles contained in the Declaration of Helsinki.

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