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Initial experience with carboplatin desensitization: A case series in a paediatric hospital

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To the Editor:

For several years, carboplatin has been the most efficacious and safest first-line treatment for paediatric low-grade gliomas (LGGs), although very recently vinblastine has been proven to display a better safety profile with similar efficacy (1). Classically, hypersensitivity reactions to carboplatin appeared in around 27% to 42% of cases (2). These reactions are especially frequent as of the seventh cycle (3) in adults and the ninth in children (4), leading to treatment withdrawal and the use of second-line drugs. Additionally, carboplatin administered in association with vincristine has been found to be a risk factor for adverse events (5), raising the incidence to 68% of children treated. In response, carboplatin desensitization has been used with great success as an alternative to treatment withdrawal in adults (3,6), allowing the patient to benefit from this drug. The evidence in children is far more limited, however, and in some cases poorer efficacy has been reported (5). In this manuscript we describe the initial experience with carboplatin allergy and desensitization in a paediatric tertiary hospital in Madrid, Spain.

The main objective of this work is to describe a prospective series of carboplatin-allergic children desensitized to carboplatin following a standardised protocol. The total number of patients treated with carboplatin, from March 2014 (first carboplatin-allergy case referred to the allergy department) to September 2016 (end of the last desensitization), were identified from electronic medical records in the hospital's pharmacy department, where all carboplatin treatments are prepared. All patients had low-grade gliomas, and all but one (Table 1) received carboplatin at a dose of 550 mg/m² along with vincristine, in accordance with the SIOP LGG 04 Protocol (7).

A detailed allergy history was obtained for patients with a potential carboplatin allergy assessed in the allergy department. Adverse events were classified according to Brown et al. (8), and all patients underwent skin prick (SPT) (10 mg/mL) and intradermal testing (ID) (1 mg/mL and 10 mg/mL) for hypersensitivity to carboplatin as previously described (3).

All were desensitized in the intensive care unit according to a standardised, slightly modified version of the classical 12-step protocol for carboplatin desensitization published by Castells et al. (3). Briefly, 3 different solutions (1/100, 1/10, and 1/1) were employed: the first solution was administered at rates of 2, 5, 10, and 20 mL/hour; the second at 5, 10, 20, and 40 mL/hour; and the third at 10, 20, 40, and 80 mL/hour. Each step lasted 15 minutes, with the exception of the final infusion, which continued until the full carboplatin dose was delivered (174 minutes), for a full treatment duration of 5 hours and 39 minutes. The carboplatin dose interval was 4 weeks, as recommended by the hospital oncologists.

All patients were pre-medicated with oral dexchlorpheniramine and methylprednisolone (1 mg/kg) administered 1 hour before the carboplatin infusion began. According to standard oncology protocols, all patients were hyperhydrated at 3 L/m² and given antiemetic ondansetron before chemotherapy.

In the 2.5-year period reported, 6 of 7 (85.7%) patients receiving carboplatin had a reaction compatible with carboplatin hypersensitivity, 5 of whom were referred to the allergy department for carboplatin desensitization. One of the 6 patients reacting to carboplatin did

not exhibit a significant improvement with carboplatin therapy, and after the index reaction (IR) the treatment was withdrawn, and a second-line therapy was established. The median age of the subjects was 5 years (yo) (range, 17 months–14 yo) and 71.4% were boys (Table 1). Only 1 patient was atopic (P3, allergic rhinitis), representing 16.6% of the whole population.

A median number of 10.5 (range, 6–12) doses of carboplatin were administered until the IR, most occurring only a few minutes after the initiation of the infusion. All these reactions were considered to be suggestive of carboplatin allergy, and another drug would have been substituted for carboplatin had the desensitization not been carried out. Most of the IRs presented by the desensitized patients were mild (3 cases of grade 1), although moderate to severe reactions were also identified (1 grade-2 and 1 grade-3 reaction) (Table 1). Unfortunately, tryptase determinations were not obtained for any of the cases. None of these events were treated with adrenaline. As each chemotherapy treatment was given at 4-week intervals, all skin and intradermal tests were performed within 2 to 3 weeks after the IR, and all were negative.

In total, 31 desensitizations were carried out and all were successfully completed; 2 patients (P2 and P4) tolerated all courses well. Five adverse events were recorded in 3 patients (P1, P4, and P5), representing 16.1% (n=5) of all cycles. Four adverse events were mild, and the 1 mild-moderate event, which occurred in the patient who also developed the most severe IR (P4, Table 1), was resolved with prompt administration of intramuscular adrenaline. These adverse reactions were managed by discontinuing the infusion and administering rescue medication (Table 1), with intravenous dexchlorpheniramine being the most frequent drug prescribed. Once the reaction was controlled, the infusion was resumed until the full dose was achieved, in all cases without further problems.

All reactions occurred at the initiation of the twelfth step (highest concentration, 80 ml/h), and in most cases in the second or third course of desensitization. In patient 1, the protocol was slightly modified after the third reaction occurred at the same stage. An intermediate step consisting of 60 mL/hour administered for 15 minutes was added prior to the last 80mL/h phase, without further reactions in this patient.

In our cohort of 7 patients treated with carboplatin, 6 (85.7%) had an adverse event related to this drug, 5 of whom underwent desensitization and subsequently were able to receive 100% of the remaining doses in their pre-established oncology-management plan.

In the past few years, some reports of carboplatin desensitization in the paediatric population have been published, with different degrees of success (76%, n=56 (9) and 20%, n= 10 (5)). Although ours is a small case series, it is the most successful of those published in children. It should be taken into account that our study has a shorter recruiting period of only 2.5 years, compared to others, where time spans of 10 years or longer are described (4,9). However, one strength of the present work is its prospective design, which contrasts with others that are based on retrospective data.

As expected, adverse reactions arose during the treatment, affecting 60% of the treated population. None of these 5 events were severe, and only 1 can be considered mild to moderate, although it was quickly controlled with the use of adrenaline. As described in other publications (3), adverse events occurred when the highest infusion rate and dilution were used.

Our 100% success rate should be put in context alongside other protocols with poorer success despite the fact that other reports contain lower (175 mg/m² vs 550 mg/m²) (4) carboplatin doses, which could potentially be easier for patients to tolerate. The paediatric-based publication that most closely resembles ours in terms of dose and study period is that of Dodgshun et al. (5), in which patients were recruited over only 2 years and treated with a high-dose carboplatin scheme. The authors report poor efficacy, with just 2 out of 10 (20%) carboplatin-allergic subjects achieving successful desensitization, most likely due to protocol-based differences relative to other publications. Our treatment is based on sequential delivery of the drug, which has previously been shown to block the release of pre-formed mediators in mast cells, (10), whereas in Dodgshun et al (5), a single flow rate was used in each of the dilutions, which may have precluded the pro-tolerogenic effect of incremental doses and infusion rates.

In studies reporting on adult subjects, carboplatin skin tests are usually performed with positive results (88%–100% (3,11)) in most cases. In our small series, none of our patients showed positive skin tests. A possible explanation is that, as has been described previously (12), the best time frame to perform these tests is 6 weeks to 6 months after the IR. Since our tests were obtained only 2 to 3 weeks after the reaction, a potential period of anergy might have precluded the chance to obtain positive results. Alternatively, paediatric subjects could behave differently and display positive results less frequently; however, there is scant information regarding skin testing in paediatric subjects. This trend in paediatric studies to avoid the use of these tests (4,5) without a clear underlying rationale is noteworthy. A possible explanation may be that adult studies are usually performed by allergists, who use skin tests in their daily routine, whilst paediatric oncologists may not feel the need to perform them.

Risk-assessment plans are nowadays a crucial part of optimising management of subjects who develop adverse events in the course of chemotherapy. Aiming to desensitize only true carboplatin-allergic patients, Madrigal-Burgaleta et al. (13) describe a flow chart in which patients with mild IR and either negative skin tests and/or negative carboplatin graded challenges are not desensitized, revealing that only 1 out of 6 potential candidates are in real need of the treatment. Shah et al. (9) report successful re-challenge with “precautionary measures” (prolonged infusion and premedication) in 40 out of 55 children (73%) who had suffered a previous adverse reaction to carboplatin, although almost half of these (19, 47.5%) required desensitization in later stages of their treatment.

The most relevant weakness of our report concerns whether all desensitized patients were real allergic patients or not. We found an unusually high incidence of carboplatin reactions (87.5%) compared to that of other series (38.9% or 41.9%) (9, 2). In addition, none of them displayed positive skin tests that could have supported their allergic status, and none were re-exposed to the drug outside the desensitization procedure. However, 3 out of our 5 patients suffered adverse reactions during desensitization, providing a certain degree of evidence that at least these 3 subjects were carboplatin-allergic. For the remaining 2 patients with good carboplatin-desensitization tolerance, one had a grade-2 IR, which supports the use of desensitization to some extent. Finally, patient number 3, with mild IR and no adverse events throughout the protocol, may not have needed desensitization.

The rationale for our approach in our inexperienced centre was to use the safest protocol, avoiding diagnostic challenges, using the intensive care unit as a precautionary setting, and providing patients with full premedication. Our good results in terms of efficacy and safety may encourage other inexperienced centres, and could be useful in expanding this treatment to other departments where it is currently not being used. Based on the knowledge and positive results achieved, our future patients will benefit from optimised treatment, including a re-challenge assessment in those with milder reactions for better selection of the patients needing the treatment, and shorter schemes, as seen in work carried out by other authors in adult populations (11,13).

In conclusion, we report our 2.5-year experience in paediatric low-grade glioma patients treated with carboplatin desensitization. We have observed 85.7% prevalence of carboplatin hypersensitivity and obtained 100% success in the 5 patients treated with carboplatin desensitization. Our results may encourage other inexperienced allergy departments to begin providing this treatment to both oncologists and patients.

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Table 1. Patients undergoing carboplatin treatment in the study period

P	Age, gender	Carboplatin dose (mg/m ²); dose triggering IR	Grade and IR characteristics and treatment	Number of desensitization	Description of desensitization-related adverse events
1	1 year, 5 months. M	550; 6	Grade 1: After a few minutes of infusion, ocular and nasal pruritus with facial erythema. Dexchlorpheniramine	7	R1, mild: 2 nd desensitization: 10 minutes after the 12 th step, facial erythema, hives in nasogenian fold, and pruritus treated with dexchlorpheniramine. R2, mild: 3 rd desensitization: 10 minutes after the 12 th step, facial erythema, hives, and pruritus treated with dexchlorpheniramine. R3, mild: 4 th desensitization: 5 minutes after the 12 th step, facial erythema, hives, and pruritus in nasogenian fold treated with dexchlorfeniramine.
2	2 years, 9 months. M	550; 7	Grade 2: Immediately after (5 min) the initiation of the infusion the patient presented with cough, facial and abdominal erythema, and pruritus. Dexchlorpheniramine	9	No adverse events
3	5 years. M	550; 10	Grade 1: After a few minutes of infusion, developed facial and thorax erythema and pruritus. Dexchlorpheniramine	6	No adverse events
4	5 years. F	550; 11	Grade 3: Cough, rhinorrhea, generalized erythema, and hives with oxygen desaturation. Dexchlorpheniramine and methylprednisolone	4	R1, moderate: 2 nd desensitization: 2 minutes after the 12 th step, generalized erythema and mild pruritus treated with dexchlorpheniramine. After 10 minutes the reaction worsens and the patient complains of moderate pruritus with some hives around the whole body and rhinitis. Intramuscular adrenaline is administered with full control of the reaction.
5	14 years. M	550; 12	Grade 1: After full infusion, developed ear, facial, and palmoplantar erythema, and pruritus. Dexchlorpheniramine and methylprednisolone	5	R1, mild: 3 rd desensitization: 10 minutes after the 12 th step, chest erythema and nausea, controlled by simply stopping the infusion
6	4 years, 7 months. M	550; 12	Grade 2: Immediately after full infusion, face and thorax erythema and oxygen desaturation. Dexchlorpheniramine and methylprednisolone	NP due to carboplatin, failed neoplasm control	NA
7	1 year. F	18.3; NA	NA	NP	NA

Classification provided according to Brown SG et al. J Allergy Clin Immunol 2004. P: Patient; M: male; F: female; LGG: low grade glioma; IR: index reaction; NP: not performed; NA: not applicable. All patients showed negative SPT and ID. Age is given for the time when the cancer diagnosis is established. Regardless of appearance of adverse events, all doses were fully administered. Infusion at the 12th step was performed with the highest concentration infusion at a rate of 80 ml/h.