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.[1]

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

Carboplatin is used for the treatment of a wide range of tumours and the combination with vincristine is the most widely adopted scheme for childhood low-grade glioma (LGG).[2]

The aim of this letter is to report a 10-year period 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.

Usually, pre-medication with steroids and antihistamines combined with a slower infusion rate was tried by oncologists in mild cases.

Skin prick tests (10 mg/mL) and intradermal tests (1 and 10 mg/mL) with carboplatin were performed according to international recommendations.[3]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.

All patients were desensitized under close supervision of allergists. In milder cases, RDDs were performed in the paediatric oncology day hospital/ paediatric 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[4]; subsequently the protocol developed by Castells [3]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 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^2) 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 were 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). Tryptase was measured in only 6 of 9 patients with anaphylaxis and was elevated (>11,4 ng/mL) in 2. Only one patient received epinephrine.

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

No schedule delays due to desensitisations 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 premedication 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 was unsuccessful due to severe BRs despite adaptations and an alternative drug was used.

Discussion

Literature data on carboplatin HSRs in children with LGG is limited. The higher rate of HSRs was found in the cohort of *Dudgshun et al*[5]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 include patients that tolerated subsequent infusions after preventive measures were started, and this may explain the results´ difference as only 1/3 of *Dodgshun´*s patients were desensitized with carboplatin.

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

Anaphylaxis represented 60% of the IR, in agreement with the literature which report that most of platinum HSRs are severe. [8]

Only one patient was treated with adrenaline, which emphasizes the worldwide reality in which anaphylaxis is often under recognized and under-treated. [9]

ST to carboplatin have been recommended between the fifth and eight cycle in order to predict the risk of future HSR. [10]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 (6 weeks to 6 months after the IR) would imply a treatment delay. Of the 4 patients tested, only one had a 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.[11] Validation of ST with EMLA® with other drugs found no differences in ST results but platins were not evaluated in this study.[12]

Although only one of the suspected HSR was confirmed by ST, the high rate of BR during RDD (60%) corroborates the initial diagnosis.

Only 2patients (13%) failed RDD. They had bothersome symptoms that persisted or even worsen 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 [3]in adult series, but significantly different from some of paediatric series with higher success rates observed in milder reactions or lower carboplatin doses. [1, 5-7, 11]

The SIOP guidelines [2] discourages RDD to carboplatin; nevertheless RDD has been successfully performed in our department as in several other centres. [4, 6, 7, 11]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 paediatric oncology center.

RDD were 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 includes the small number of patients and the absence of all data in some patients due 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.

Key-words: desensitization, carboplatin, low-grade glioma, chemotherapy, anaphylaxis

Josefina Cernadas*[1,2] Maria João Vasconcelos*[1], Ana Paula Fernandes[3], Leonor Carneiro-Leão[1,2,] Maria João Gil-da-Costa[3]

*These authors contributed equally to the writing of the manuscript

In relation to this manuscript, the authors declare no conflicts of interest.

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

1. Serviço de Imunoalergologia, Centro Hospitalar Universitário de São João, Porto, Portugal
2. Unidade de Imunoalergologia, Hospital dos Lusíadas, Porto, Portugal
3. Serviço de Oncologia Pediátrica, Centro Hospitalar Universitário de São João, Porto, Portugal

1. Turgay Yagmur, I., et al., *Evaluation of hypersensitivity reactions to cancer chemotherapeutic agents in pediatric patients.* Ann Allergy Asthma Immunol, 2020.
2. *National Cancer Institute. Clinical trial. Available at URL: http://www.cancer.gov/search/ViewClinicalTrials..aspx?cdrid5454506&version5patient&protocolssearchid53447647. Accessed July 5, 2007.*
3. Castells, M.C., et al., *Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases.* J Allergy Clin Immunol, 2008. **122**(3): p. 574-80.
4. Confino-Cohen, R., et al., *Successful carboplatin desensitization in patients with proven carboplatin allergy.* Cancer, 2005. **104**(3): p. 640-3.
5. Dodgshun, A.J., et al., *Carboplatin Hypersensitivity Reactions in Pediatric Low Grade Glioma Are Protocol Specific and Desensitization Shows Poor Efficacy.* Pediatr Blood Cancer, 2016. **63**(1): p. 17-20.
6. Genc, D.B., C. Canpolat, and S.G. Berrak, *Clinical features and management of carboplatin-related hypersensitivity reactions in pediatric low-grade glioma.* Support Care Cancer, 2012. **20**(2): p. 385-93.
7. Shah, A.C., et al., *Carboplatin Rechallenge After Hypersensitivity Reactions in Pediatric Patients With Low-Grade Glioma.* Pediatr Blood Cancer, 2016. **63**(1): p. 21-6.
8. Pradelli, J., et al., *Allergy Evaluation of Hypersensitivity to Platinum Salts and Taxanes: A Six-Year Experience.* J Allergy Clin Immunol Pract, 2020.
9. Grabenhenrich, L.B., et al., *Epinephrine in Severe Allergic Reactions: The European Anaphylaxis Register.* J Allergy Clin Immunol Pract, 2018. **6**(6): p. 1898-1906 e1.
10. Markman, M., et al., *Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity.* J Clin Oncol, 2003. **21**(24): p. 4611-4.

11. Rodriguez Del Rio, P., et al., *Initial experience with carboplatin desensitization: A case series in a paediatric hospital.* Pediatr Allergy Immunol, 2018. **29**(1): p. 111-115.
12. Couto, M., et al., *Intradermal Tests for Diagnosis of Drug Allergy are not Affected by a Topical Anesthetic Patch.* Allergy Asthma Immunol Res, 2014. **6**(5): p. 458-62.