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Mini-Review

Carboplatin-related toxicity in children with cancer

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ABSTRACT

Carboplatin is characterized by a subcellular mechanism of action similar to that of cisplatin although its clinical spectrum of side effects differs somewhat from that of cisplatin. Its half-life is 170 ± 34 minutes and is independent of dose; myelosuppression represents its dose-limiting toxicity. Many studies have shown that carboplatin has no clinically apparent nephrotoxicity or neurotoxicity; therefore, carboplatin may be an alternative to cisplatin in clinical circumstances where the renal or neural toxicities are dose-limiting considerations. In patients with normal renal function, carboplatin can be administered up to 600 mg/sqm with leukopenia and thrombocytopenia reversing within 14 days of drug administration. In our review, we describe the pharmacological profile and the toxicities related to the use of carboplatin for the treatment of children with cancer.

KEYWORDS: carboplatin, hypersensitivity, toxicity.

1. Introduction

The use of platinum compounds for the chemotherapy treatment of pediatric cancers has extended the long-term survival of these patients.

Carboplatin is a second-generation derivative of platinum, often used instead of cisplatin which was the first drug in this class to be synthesized. It has a spectrum of activity and efficacy similar to cisplatin, despite this, it seems to have less incidence of neurotoxicity, nephrotoxicity, and nausea; the main side effect is myelosuppression [1].

In children, carboplatin is used to treat neuroblastoma, germ cell tumors, hepatoblastoma, and different types of brain tumors (low-grade glioma, medulloblastoma, PNET) [2-4].

Unfortunately, potential side effects related to the use of carboplatin can have a negative impact on the quality of treatment and on the life of children with cancer [5, 6].

2. Structure

Carboplatin is an analog of cisplatin developed to reduce the dose-dependent toxicity of cisplatin (Figure 1) [7]. Carboplatin has greater chemical stability than cisplatin, and is, therefore, less reactive with DNA but also less toxic than cisplatin [8]. Previous studies have shown that carboplatin is 8 to 45 times less potent than cisplatin and in order to achieve comparable anticancer effects, carboplatin should be administered in higher doses [9, 10]. This is probably due to its weaker effect in damaging the double-helix structure of DNA.

As for its structure, cis-diamine 1,1-cyclobutane-dicarboxylate CBDCA, platinum has an outgoing cyclobutane-dicarboxylate group that facilitates a slow reaction with antioxidant molecules such as glutathione and metallothionein. The mechanism of action of carboplatin is similar to that of cisplatin: the drug binds covalently to DNA,

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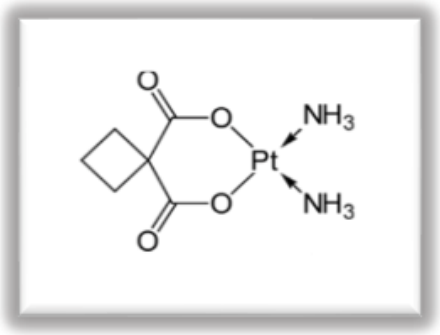

Figure 1. Structure of the carboplatin.

causing chain alkylation; however, carboplatin is found to be weaker in causing DNA damage because it produces DNA adducts more slowly [9-11].

Within the cell, a slow conversion of carboplatin into reactive species occurs, which then form cross-bonds of DNA molecules that inhibit synthesis [11-13].

3. Pharmacokinetic

Due to its chemical structure, carboplatin has less binding to plasma proteins (Table 1). Its half-life is 170 ± 34 minutes and is independent of the dose administered. As for the elimination of the drug, about 90% is excreted unmodified by the kidneys within 24 hours; the renal elimination of carboplatin is almost reached exclusively by glomerular filtration. Therefore, the drug passage is closely related to glomerular filtration rate (GFR) and the latter is related to carboplatin AUC (area below the concentration-time curve), which describes systemic exposure to the drug and correlates with its clinical efficacy and toxicity, especially myelosuppression and emesis [8, 12-16]. Creatinine clearance is routinely adopted to evaluate the GFR, although the preferred method would be to use an isotope tracer such as 51Cr-EDTA [13, 17-19].

4. Toxicity

4.1. Ototoxicity

A substantial part of the literature suggests that carboplatin is less ototoxic than cisplatin (Table 2) [8, 13, 19-22]. As reported in numerous studies, the use of non-myelopathic doses of carboplatin generally does not cause ototoxicity [20, 23-25].

When carboplatin is administered at the myelopathic doses in alternating cycles with cisplatin, after chemotherapy with cisplatin or in combination with osmotic agents (such as mannitol) altering the blood-brain barrier, it may cause significant ototoxicity [23, 25-29].

4.2. Myelosuppression

Myelosuppression is the dose-dependent toxicity of carboplatin.

Go and Adjei report that severe thrombocytopenia is detected in 25% of patients exposed to the drug, while severe neutropenia occurs in 18% of cases [13]. Despite this, infectious complications and bleedings are rare [30].

Anemia is most frequently observed with increased exposure to carboplatin [8]. O'Dwyer *et al*. report that platelet counts reach their lowest point from 17 to 21 days after a single dose of carboplatin [9].

Several studies have shown that carboplatin myelotoxicity is strongly associated with AUC (area under the curve) and drug clearance is directly proportional to GFR [8, 9, 31-35].

4.3. Nephrotoxicity

Carboplatin-dependent dose nephrotoxicity is more common in the presence of previous or concomitant nephrotoxic therapies or when high doses of carboplatin are associated with melphalan, vincristine, and etoposide for the rescue of autologous bone marrow [32, 33, 36, 37]. High cumulative doses of carboplatin have been associated with a slight decrease of the GFR and serum magnesium, although their impact is not relevant for the clinical practice.

4.4. Nausea and vomiting

Nausea and vomiting due to carboplatin are much less frequent and severe than those associated with cisplatin (Table 2), and easily controllable with the administration of standard antiemetics (dexamethasone and ondansetron ± lorazepam) [8, 13, 38, 39].

4.5. Hypersensitivity

Multiple carboplatin exposures may cause hypersensitivity reactions (HSR), leading to early

Table 1. Pharmacokinetic characteristics of carboplatin.

Pharmacokinetic characteristics	Cisplatin	Carboplatin
Protein binding (%)	>90	25-50
Terminal half-life (h)	24-127	8.2-40
Urinary output (%)	23-50	54-82

Table 2. Carboplatin and cisplatin toxicity.

Platinum compound	Ototoxicity	Myelosuppression	Neurotoxicity	Nephrotoxicity	Nausea/ Vomiting
Cisplatin	+		+	+	++
Carboplatin		+			+

cessation of treatment [5]. In 2012, Patil *et al.* reported that the range of incidence of reactions ranged from 7 to 59% [40].

The risk of hypersensitivity appears to be related to the cumulative number of infusions, rather than the cumulative dose, and grows with repeated exposure to carboplatin; it is generally expected after 6 or more rounds of chemotherapy. This seems to increase with the number of infusions in patients receiving weekly infusions rather than monthly carboplatin [41, 42]. A higher risk of HSR is also associated with an earlier history of allergy to other drugs. Previous studies have identified weekly carboplatin infusions, young people, and women as risk factors for allergic reactions in children with brain cancer [43-47]. No significant correlation was found between the onset of HSR and previous surgery, radiotherapy, or tumor localization [40]. Carboplatin generally induces mild or moderate hypersensitivity reactions (cutaneous erythema, facial edema, and redness, abdominal pain, diarrhea, wheezing, bronchospasm, tachycardia, hypo/hypertension) which occur a few minutes after the start of the infusion and also continue several hours after the withdrawal of the drug. Early manifestations are probably caused by a type I IgE-mediated hypersensitivity mechanism; but also the type IV mechanism appears to be present in the pathogenesis of the reaction, occurring hours or days after infusion [5]. Pretreatment with steroids or antihistamines usually fails in preventing IgE-mediated reactions.

The effectiveness of oral antihistamines has been established only in cases of mild or moderate hypersensitivity; in addition, prolonged steroid use in children and adolescents is associated with severe side effects. Therefore, in children with carboplatin HSR or positive skin test, in the absence of severe hypersensitivity, the possible treatment options are desensitization, discontinuity of therapy, or transition to cisplatin [5, 43].

The substitution of carboplatin with cisplatin may be limited by a cross-reaction of specific IgE platinum, but there are not enough studies to define the actual incidence [48-50].

The benefit of continuing treatment with carboplatin should be considered in relation to the risk of more severe hypersensitivity reactions. In cases of severe HSR, the treatment with platinum compounds is usually suspended. The current International Society of Pediatric Oncology (SIOP) protocol for the treatment of low-grade gliomas (LGG) discourages the application of desensitization in an attempt to continue carboplatin therapy and recommends alternative drug combinations [49, 51-54]. However, the combination of vincristine and carboplatin is characterized by a high response rate in the treatment of children with LGG. Consequently, a desensitization protocol was considered appropriate

in order to safely reintroduce carboplatin without the risk of recurrent HSR. “Rapid drug desensitization” (RDD) is a procedure described in order to obtain temporary clinical tolerance to the drug [42, 48]. It consists of the administration of the total dose of the drug in sequential increments, in order to obtain an inhibition of the activation of the mast cells for the specific pharmacological antigen. It would seem possible that the administration of small progressive increments could lead to the consumption of IgE antibodies without the occurrence of acute reactions. The rapid desensitization could allow patients with HSR to be treated with first-line chemotherapy, ensuring a better impact on the quality of treatment and long-term survival [50, 55-65].

5. Conclusions

In children with cancer, the adoption of carboplatin in the armamentarium treatment strategy is relatively frequent: in such patients, an accurate clinical and laboratory monitoring is essential in order to allow the early detection and appropriate treatment of any carboplatin-related toxicity.

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CONFLICT OF INTEREST STATEMENT

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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