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Mini-Review

Hypersensitivity reactions to platinum drugs

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ABSTRACT

Platinum compounds (cisplatin, carboplatin, and oxaliplatin) are a category of chemotherapeutics widely used in the therapy of various cancers because of their high efficacy and tolerability. Cases of hypersensitivity reactions to these compounds have increased in recent decades due to their frequent use. Carboplatin is the platinum compound associated with the highest incidence of immediate hypersensitivity reactions. It is critical for clinicians to be familiar with allergy diagnostics and to correctly diagnose immediate hypersensitivity reactions to platinum compounds and to identify sensitized patients to both reduce the risk of severe reactions and to continue effective chemotherapy treatment.

KEYWORDS: hypersensitivity, desensitization, platinum compounds.

1. Introduction

Platinum coordination compounds are a category of antineoplastic drugs that contain a platinum atom. Three different compounds have been identified: cisplatin, carboplatin, and oxaliplatin [1-3]. Cisplatin was the first platinum compound to be synthesized in 1965. Structurally, this chemotherapeutic consists of a central platinum atom surrounded by two chlorine atoms and two ammonium atoms. Cisplatin, which is available as a solution for infusion, is used alone or in combination with other drugs for the treatment of various cancers in both adults and pediatric patients. Carboplatin is a second-generation platinum compound. Unlike cisplatin, it can also be administered in patients with impaired kidney function. It is used instead of cisplatin for the treatment of many types of cancer because of its lower toxicity. Oxaliplatin, on the other hand, represents the third generation of platinum compounds. The mechanism of action of platinum compounds is based on their ability to form intra- or inter-chain bonds in cellular DNA and thus inhibit cell replication and induce cell death by apoptosis [2].

However, these drugs are associated with possible side effects. In particular, cisplatin is the drug with the most side effects, including vomiting, hematologic toxicity, nephrotoxicity, ototoxicity, and neurotoxicity [4, 5]. The side effects of carboplatin and oxaliplatin are less severe than those of cisplatin; in fact, they do not induce nephrotoxicity, except at high doses, but are equally associated with emesis, hematologic toxicity, and neurotoxicity both acute and chronic [6-11]. Adverse reactions to platinum compounds include hypersensitivity reactions, defined as unexpected reactions that cannot be explained by the toxicity profile of the drug [6]. Adverse drug reactions, including reactions to platinum compounds, are classified by the WHO into type A reactions and type B reactions [12]. Type A reactions are predictable reactions caused by the structure of the drug and its mechanism of action. These reactions may also result from overdose of

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the drug or interaction with other drugs. Unlike Type A reactions, Type B reactions are caused by mechanisms independent of the drug's toxicity, can occur even at low doses, and are often unpredictable reactions. Approximately 20% of adverse drug reactions are Type B reactions, and most of these reactions are the result of the activation of immunologic mechanisms. There is, however, a proportion of Type B reactions whose mechanisms have not yet been elucidated [13, 14]. Clinically, drug hypersensitivity reactions are distinguished into immediate reactions and non-immediate or delayed reactions depending on the time between drug exposure and the onset of clinical manifestations. Immediate reactions occur within 1 hour after drug administration; they are generally induced by an IgE-mediated mechanism and the clinical manifestations may affect different organs (skin, respiratory system, gastrointestinal system, eyes, nose, etc.) with the appearance of urticaria, angioedema, bronchospasm, gastrointestinal symptoms such as nausea, vomiting, diarrhea, abdominal pain, conjunctivitis, rhinitis, up to severe systemic reactions such as anaphylactic shock [15-22]. Delayed reactions can occur at any time from one hour after drug exposure. These reactions are T-cell mediated and are clinically characterized by maculo-papular eruptions, eczema, and urticaria-like exanthems [16]. It should be kept in mind that the same drug can induce both immediate and delayed reactions [17]. Hypersensitivity reactions to platinum compounds are life-threatening adverse reactions that often require discontinuation of treatment or replacement of the therapeutic regimen with another chemotherapeutic agent, with possible negative consequences on the patient's quality of life and survival [23-25].

2. Incidence

Hypersensitivity reactions to platinum compounds are increasing both because these drugs are widely used in the treatment of a wide variety of malignancies, and because the increased life expectancy of cancer patients means that the same patient will encounter repeated exposure to the same category of drug. Knowing the incidence of hypersensitivity reactions to platinum compounds and the associated risk factors is essential for diagnosis and to avoid severe reactions in patients. The incidence of these reactions increases with exposure and the number of treatment cycles the patient undergoes [2].

Carboplatin is the platinum compound associated with the highest incidence of immediate hypersensitivity reactions; the incidence depends on the number of cycles of carboplatin-based chemotherapy the patient received, ranging from an incidence of 1% for those who received 5 or fewer cycles, to 6.5% for those who received 6 cycles, 7% for those who received 7 cycles to 19.5% for those who received 8 cycles of chemotherapy [26-28]. The incidence of reactions to cisplatin is reported in the literature to be around 5%, probably due to the lower use of this compound as first-line therapy.

The incidence of reactions to oxaliplatin is reported to be around 13%, of which 0.5% are reactions defined as severe [27, 29]. However, some difficulty is recognized in assessing the true prevalence of reactions to oxaliplatin because of the variability in its clinical presentations [2].

3. Risk factors

Numerous studies have attempted to identify potential risk factors for the development of immediate hypersensitivity reactions to platinum compounds. Several studies show that the risk of developing an immediate hypersensitivity reaction increases consensually with the number of patient exposures to the platinum compound. For carboplatin and cisplatin, sensitization occurs after an average of 8 cycles of chemotherapy [30]. Another risk factor is represented by previous treatment with a different platinum compound: in fact, it has been reported in the literature that among women with ovarian cancer treated with carboplatin, 22.2% of patients who developed an immediate hypersensitivity reaction to carboplatin subsequently presented an immediate hypersensitivity reaction to cisplatin as well [26]. Additional risk factors are atopy (genetic predisposition to the development of allergic diseases) and a previous history of hypersensitivity reactions during therapy with other drugs. Mutations in the BRCA1 and BRCA2 genes have also been reported to present a risk factor for developing hypersensitivity

reactions in patients with recurrent gynecologic malignancies undergoing carboplatin-based regimens. Finally, age (younger patients show a higher risk) and a high cumulative dose of carboplatin have also been identified by some studies as risk factors for the development of immediate hypersensitivity reactions to carboplatin [2].

4. Clinical manifestations

Most hypersensitivity reactions induced by platinum compounds occur during or immediately after drug administration and are classified as type I or IgE-mediated hypersensitivity reactions.

The clinical manifestations presented during immediate hypersensitivity reactions are the consequence of IgE-mediated activation of mast cells and/or basophils. This mechanism is supported by the immediate onset of symptoms during drug administration or shortly thereafter (within 1 hour of administration); previous exposure to the drug (sensitization); and the possible positivity of skin tests. Activation of mast cells and/or basophils can be supported by the finding of elevated values of tryptase, a serine protease preformed in the granules of these cells and released after their activation. Due to the short half-life of this mediator, its presence in the circulation can be assessed within about 2 hours after drug administration. It is also important to keep in mind that activation of mast cells and/or basophils can also occur following a non-IgE-mediated mechanism and the clinical manifestations can be similar to those of IgE-mediated activation. If the reaction nevertheless occurs during the first administration, it is likely that the mechanism of activation of these cells was caused by a non-IgE-mediated mechanism because the subject was not previously sensitized to the drug [31-34]. The most frequent symptoms and signs during such immediate reactions are cutaneous manifestations: appearance of erythema and palmar itching, urticaria and rash (99%). Respiratory symptoms are also very frequent (cough, dyspnea, bronchospasm) (30%). As additional symptoms, gastrointestinal disorders (nausea, vomiting, diarrhea) (26%), hypotension (11%) or hypertension (11%), and more rarely feeling of throat closure, abdominal or chest pain were observed [2, 15].

5. Diagnosis

5.1. Skin tests

Skin tests (skin prick tests and intradermal testing) are the ideal tool for the diagnosis of immediate hypersensitivity reactions to platinum compounds. Overall, the sensitivity of skin tests for the diagnosis of immediate hypersensitivity reactions to carboplatin is around 80%.

However, the false-negative rate of skin tests for carboplatin ranges from 8% to 8.5%; patients whose clinical history is suggestive of immediate hypersensitivity reaction but more than 6 months after the date of skin testing often convert from negative to positive skin tests after re-exposure to the drug [35-40]. Therefore, caution should be exercised in interpreting a negative skin test in patients who have not been exposed to platinum for more than 6 months because the sensitivity may be less than 36% compared with the 83% sensitivity that the skin test has when the allergic reaction is recent (less than 6 months) [35, 40].

Skin tests can be used to preemptively identify patients at risk of developing a hypersensitivity reaction to platinum compounds. For carboplatin, good negative predictive values have been demonstrated in several studies: values from 99% to 92% when patients who had received at least 6 previous carboplatin treatments were evaluated [35, 41]. Skin testing should be performed at least 2 weeks after the onset of the hypersensitivity reaction. Control by skin testing should begin with a skin prick test performed on the volar surface of the forearm with the undiluted drugs in the doses: 1-10 mg/ml for carboplatin; 1-5 mg/ml for oxaliplatin; 1 mg/ml for cisplatin. The test is considered positive when a wheal of at least 3 mm is determined 20 minutes after execution. In addition, the test is also examined after 6, 24, and 48 hours [35, 40, 42]. Intradermal tests are performed using a sterile solution of each drug, sequentially diluted (10-3, 10-2, 10-1) in 0.9% saline, then using a concentration up to a maximum of: 10 mg/ml for carboplatin; 5 mg/ml for oxaliplatin; 1 mg/ml for cisplatin. For intradermal testing, a 2-fold increase in the diameter of the initial wheal 20 minutes after intradermal injection is considered positive. The wheal is also examined after 6, 24, 48, and

72 hours [42, 43]. Based on literature data, patch tests do not appear to have diagnostic value in delayed hypersensitivity reactions to platinum compounds [35, 42].

5.2. Specific IgE

Platinum-specific IgE can be measured in patients exposed to treatment with platinum compounds using the ImmunoCAP system. Pagani *et al.* reported that in three patients with carboplatin hypersensitivity and positive skin tests, it was possible to detect carboplatin-specific IgE, but in one of them cisplatin-specific IgE was also present, which had however never been administered to these patients, thus demonstrating the possible cross-reactivity between the two compounds [43-45]. However, the specific IgE assay is not a routinely performed test in the management of patients with hypersensitivity to platinum compounds because it has not yet been validated [35].

6. Desensitization protocols

Drug desensitization is the induction of a temporary state of clinical insensitivity/tolerance to a drug responsible for a hypersensitivity reaction. Desensitization should be considered when the drug responsible for the hypersensitivity reaction is essential to the treatment of a disease. It is also sometimes necessary in treatments with platinum compounds when, due to the characteristics of the patient and the neoplastic pathology, there are no viable therapeutic alternatives [4]. In the desensitization procedure, the concentration of the antineoplastic drug, which acts as an antigen for the development of hypersensitivity, is slowly and gradually increased to induce a state of temporary tolerance towards the drug itself, until the target dose is reached. There is currently no standardized protocol, and hence guidelines recommend referring to existing protocols that have already been successfully applied [1, 46]. These are, therefore, protocols in which the patient is treated with increasing concentrations of the hypersensitizing drug with incremental doses of 4 to 12 progressive steps [47-49].

7. Conclusions

The frequency of hypersensitivity reactions to platinum compounds (carboplatin and cisplatin) has increased in recent decades because of their frequent use in the treatment of both adult and pediatric cancers. Hypersensitivity reactions to platinum compounds are life-threatening adverse reactions that often require discontinuation of treatment or replacement of the therapeutic regimen with another chemotherapeutic agent, with possible negative consequences on the patient's quality of life and his chances of cure and survival. In the diagnosis of immediate hypersensitivity reactions (IgE-mediated) *in-vivo* skin tests (skin prick test and intradermal test) represent the first-choice tool, recommended for initial screening, by virtue of their simplicity, rapidity, repeatability, high specificity, and low cost. However, these tests should be performed only by experienced personnel and in facilities where it is possible to intervene in case of anaphylactic reactions. Skin tests find their application not only in the diagnosis of a suspected IgE-mediated reaction, but also in the identification of subjects sensitized to the platinum compound used in therapy. This would allow the prevention of possible hypersensitivity reactions during the next line of therapy.

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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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