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Outpatient rapid 4-step desensitization for gynecologic oncology patients with mild to low-risk, moderate hypersensitivity reactions to carboplatin/cisplatin

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HIGHLIGHTS

- We developed an outpatient desensitization protocol for patients with mild to low risk moderate hypersensitivity reactions to cisplatin or carboplatin.
- Ninety-four percent patients completed outpatient desensitization protocol; ninety-nine percent desensitizations were completed in the outpatient infusion center.
- New outpatient desensitization protocol only took 1.5 to 2.25 hours for carboplatin and cisplatin.

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ABSTRACT

Objective. The primary objective of this study is to assess the efficacy and safety of an outpatient, 4-step, one-solution desensitization protocol in gynecologic oncology patients with history of mild to low-risk, moderate hypersensitivity reactions (HSRs) to platinums (carboplatin and cisplatin).

Methods. This was a single institutional retrospective review. Gynecologic oncology patients with a documented history of mild or low-risk, moderate immediate HSRs to carboplatin/cisplatin and continued treatment with 4-step, one-solution desensitization protocols in the outpatient infusion center were included. Patients with delayed HSRs or immediate high-risk, moderate or severe HSRs were excluded. The primary end point was the rate of successful administrations of each course of platinums.

Results. From January 2011 to June 2013, eighteen eligible patients were evaluated for outpatient 4-step, one-solution desensitization. Thirteen patients had a history of HSRs to carboplatin and 5 with HSRs to cisplatin. All of 18 patients successfully completed 94 (98.9%) of 95 desensitization courses in the outpatient infusion center. Eight of 8 (100%) patients with initial mild HSRs completed 29/29 (100%) desensitization courses, and 9 of 10 (90%) of patients with initial moderate HSRs completed 65/66 (94%) desensitization courses. In total, 65/95 (68%) desensitizations resulted in no breakthrough reactions, and mild, moderate and severe breakthrough reactions were seen in 19%, 12% and 1% desensitizations, respectively. No patients were hospitalized during desensitization.

Conclusions. The outpatient rapid, 4-step, one-solution desensitization protocol was effective and appeared safe among gynecologic oncology patients who experienced mild to low-risk, moderate HSRs to carboplatin/cisplatin.

Introduction

Platinums (carboplatin and cisplatin) are highly active chemotherapy agents for the treatment of patients with gynecologic cancers. However, both carboplatin and cisplatin are associated with possible hypersensitivity reactions (HSRs) [1,2]. A hypersensitivity reaction is an exaggerated or inappropriate immune response that may be localized or systemic and results in local tissue injury or changes throughout the body in response to an antigen or foreign substance [3]. The incidence of platinum hypersensitivity reactions has increased significantly in the past decade due to the extensive use of these agents, especially carboplatin [2]. The incidence of carboplatin hypersensitivity reactions in gynecologic oncology patients is 12–16%, but it can be up to 27% in patients

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that are more heavily pretreated with 7 or more courses of carboplatin [4,5]. While the incidence of cisplatin hypersensitivity reactions is 5–20% [6].

Clinical manifestations of cisplatin and carboplatin hypersensitivity reactions vary from mild to more severe, even life-threatening [7,8]. Symptoms of mild reactions include localized rash, itching and flushing, while symptoms of severe reactions often involve multiple organs and systems, including persistent hypertension, hypotension, hypoxia, bronchospasm and anaphylaxis. Approximately 50% of hypersensitivity reactions to carboplatin were considered mild [5]. Upon re-challenge, patients with history of mild HSR may develop severe HSR and onset of the symptoms often appears early [5,9].

The National Comprehensive Cancer Network (NCCN) guidelines recommend platinum desensitization for patients who have had an allergic reaction after consulting with a medical or gynecologic oncologist at centers with expertise in platinum desensitization [10]. However, no single standard desensitization protocol has been recommended [10]. Most published platinum desensitization protocols focus on patients with a history of moderate to severe HSRs and require 5 h to several days inpatient hospital setting [11–20]. Data of the management of patients with mild to moderate HSRs are limited. Jones et al. treated five patients who had mild to moderate carboplatin HSRs with cisplatin desensitization over 5 days inpatient/outpatient. Twelve of fourteen treatments were successful, but only 3 patients (60%) completed the therapy [12]. The gynecologic oncology group in our institution initiated a multidisciplinary working group to establish an outpatient protocol for patients undergoing desensitizations for mild to moderate hypersensitivities for multiple years as the standard practice. Recently, this practice was readdressed and modified to ensure the consistent highest quality of patient care across the entire cancer programs at the James Cancer Hospital/Clinics of The Ohio State University. Here we report on our retrospective experience in the efficacy and safety of an outpatient, rapid, one-solution desensitization protocol in the treatment of gynecologic oncology patients with mild to low-risk, moderate HSRs to cisplatin or carboplatin. We also assessed the incidence and severity of breakthrough reactions during the desensitization process.

Methods

Patients

Between January 2011 to June 2013, gynecologic oncology patients with a documented history of mild to low-risk, moderate immediate hypersensitivity reactions to carboplatin or cisplatin and continued treatment with one-solution, 4-step desensitizations were included. The diagnosis of hypersensitivity reactions was based on the clinical signs and symptoms, determined by the attending gynecology oncologists and discussed with the desensitization team members (chemotherapy nurses, advanced practice providers and clinical pharmacy specialist). No skin tests to platinums were done. Patients with delayed hypersensitivity reactions or immediate high-risk, moderate or severe reactions were excluded. Mild hypersensitivity reactions included localized flushing, itching and rash. Low-risk, moderate hypersensitivity reactions include diffuse erythema or urticaria, nausea/vomiting, abdominal pain and bloating, sneezing/nasal congestion, dyspnea/wheezing without desaturation, mild shortness of breath without oxygen desaturation and cough, with or without localized cutaneous reactions. Any objective measurable signs of cardiovascular, respiratory or central nervous system during the initial hypersensitivity reactions were considered high-risk, moderate or severe, with the difference of duration of these symptoms (transient vs. sustained). The study was approved by the institutional research board (IRB) of the James Cancer Hospital, The Ohio State University.

Four-step, one-solution outpatient desensitization protocol

The desensitization was conducted in the outpatient infusion center, under the supervision of the desensitization team including gynecology oncologist, clinical pharmacy specialist, nurse practitioner and clinical nurse. Based on the safety and convenience for patients, risks and benefits of desensitization were explained to all patients and consent for treatment was obtained. Patients were premedicated with H1 antagonist (diphenhydramine), H2 antagonist (famotidine 20 mg) and glucocortical steroid (dexamethasone 20 mg) all intravenously 30 min before the desensitization. Oral or intravenous lorazepam was given to patients as needed. Epinephrine injection was available. Beta-blockers were held 24 h before desensitizations.

Carboplatin doses (AUC 3–6) were calculated with Calvert formula and were prepared in the standard 500 ml normal saline piggy bag. Cisplatin was prepared in a 1000-ml normal saline bag per institution guideline. Tubing of chemotherapy bag was primed with the active drug for all patients (versus priming tubings with normal saline for patients without hypersensitivity reactions). This priming step is to ensure the accurate and consistent delivery of carboplatin or cisplatin during desensitizations. The infusion started with 50 mL/h for 15 min. If tolerated, the infusion was then increased every 15 min according to the protocol until the final step of 600 ml/h. Upon reaching the goal infusion rate, we then continued the same rate until the completion of the infusion. The details of the desensitization protocol, with an example of carboplatin 600 mg, are listed in Table 1. The total infusion time was 1.5 h for carboplatin and 2.25 h for cisplatin.

Management of breakthrough reactions

Breakthrough reactions mean reoccurring reactions during desensitizations. Symptoms of breakthrough reactions could be similar to initial reactions or involve more or less organ systems. The severity of breakthrough reactions can also vary from one desensitization to the other. If a breakthrough reaction occurred during desensitization, the infusion was immediately suspended, and intravenous diphenhydramine 25–50 mg and/or hydrocortisone 50–100 mg were administered. Intravenous famotidine 20 mg was given to patients who experienced nausea or vomiting. If the symptoms involved respiratory symptoms, 2 puffs of inhaled albuterol were administered. Once the symptoms were resolved and upon agreement of attending physicians, the infusion was resumed at the previous tolerated rate and titrated up according to the protocol. If a high-risk, moderate reaction occurred during desensitization or a mild reaction reappeared 2 more times, the attending gynecology oncologist could decide to either continue or discontinue desensitization, depending on the symptoms. In the case of severe hypersensitivity reactions or anaphylaxis, epinephrine 0.3 mg was injected, and the desensitization was discontinued. The patient would be admitted to the hospital for further management.

Statistical analysis

The primary end point was the rate of successful administrations of each course of platinums in the outpatient infusion center. Descriptive statistical analysis was performed in this study.

Results

Patient characteristics and initial HSRs

During the study period, eighteen patients in the gynecologic oncology clinic developed mild to low-risk, moderate hypersensitivity reactions to carboplatin or cisplatin and were treated on the 4-step, one-solution desensitization protocol. Thirteen patients had ovarian cancer or primary peritoneal carcinoma, 3 had endometrial cancer and