Gynecologic Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Platinum desensitization in patients with carboplatin hypersensitivity: A single-institution retrospective study

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HIGHLIGHTS

- Highlights an effective, safe and short desensitization protocol
- Allows hypersensitive patients to continue with carboplatin therapy
- Employs a straightforward home and inpatient premedication regimen
- Identifies factors that help to risk stratify patients undergoing desensitization
- Decreases the burden on health care by reducing admissions to the hospital and ICU

ARTICLE INFO

Article history:
Received 7 May 2016
Received in revised form 27 September 2016
Accepted 30 September 2016
Available online xxxx

Keywords:
Carboplatin desensitization
Gynecologic malignancy
Allergy to carboplatin
Hypersensitivity reactions

ABSTRACT

Objectives. The carboplatin desensitization (CD) protocol presented here allows patients with either a positive skin test or a prior hypersensitivity reaction (HSR) to safely, rapidly and effectively continue with carboplatin infusions. Newly described factors can identify patients at risk for developing adverse events during CD.

Methods. A retrospective review was performed on patients with gynecologic cancer who underwent CD between 2005 and 2014. The CD protocol uses a four-step dilution process over 3.5 h.

Results. 129 patients underwent CD and completed a total of 788 cycles. The desensitization protocol prevented HSRs in 96% (753 out of 788) of these cycles. Patients achieved an average of 6.1 cycles (SD ± 4.55, range 0–23) with CD. The CD protocol allowed 73% (94 of 129) of the patients to undergo carboplatin infusion without reaction. Patients with moderate to life-threatening HSRs (grade 2 through 4) were 10.5 years younger at initial CD than patients with grades 0 or 1 HSRs (52.3 vs. 63, $P = 0.0307$). One patient death occurred during her thirteenth desensitization cycle. The HSR in this case was complicated by pre-exisiting pulmonary hypertension.

Conclusions. This is the largest study of its kind showing a safe, effective and rapid (3.5 h) CD protocol. The majority of patients with a history of either carboplatin hypersensitivity reaction or a positive skin test completed the CD protocol without HSRs. Age was identified as a risk factor for HSR severity during CD. Age can be employed along with pre-load dependent cardiac conditions as a way to help risk stratify patients undergoing CD.

1. Introduction

Platinum-taxane combination regimens are used as neoadjuvant and adjuvant therapy for ovarian, uterine and cervical cancers [1]. In addition, platinum drugs have proven efficacy in the relapse setting of gynecologic cancers. Carboplatin [*cis*-diammine (cyclobutane-1,1-dicarboxylate-O,O′)platinum(II)] was approved in 1989 for the treatment of ovarian carcinoma. This platinum agent has been found to have therapeutic equivalency to cisplatin but with less emetogenesis, audio toxicity, and nephrotoxicity [2,3]. Hypersensitivity reactions to platinum compounds were first described in refinery workers inhaling complex platinum salts. These refinery workers developed respiratory (wheezing, dyspnea), gastrointestinal (cramping, diarrhea) and dermatologic (pruritus, urticaria and angioedema) reactions [4]. Patients who receive multiple doses of carboplatin chemotherapy have also been

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http://dx.doi.org/10.1016/j.ygyno.2016.09.027
0090-8258/

observed to experience these hypersensitivity reactions (HSR). The rates of HSRs in carboplatin-treated patients has shown to range between 5% and 34% [3]. Along with variable rates, carboplatin HSRs also present in a heterogeneous fashion. Some reactions develop minutes after the initiation of an infusion whereas other reactions can occur immediately following completion or days later [5]. The etiology of carboplatin HSR is currently unknown, but it is speculated that carboplatin can act as a hapten and promote a type I, IgE-mediated, histaminergic reaction. This type I response, with activation through IgE, causes a release of inflammatory molecules from basophils and mast cells (prostaglandin D2, leukotriene C4, IL-6, and tumor necrosis factor alpha) [6,7]. An alternative to the IgE-centric mechanism of carboplatin hypersensitivity is the T cell-mediated hypothesis. This type IV hypersensitivity, mediated by T cells, is a delayed reaction occuring after sensitization from multiple exposures of a noxious stimuli. A patient rarely has hypersensitivity until a critical number of cycles has been administered [5,7,8]. Additionally, patients with a history of allergy to medications or environmental stimuli have a greater potential of developing platinum HSRs, further supporting a type IV response [6–8]. With this evidence in mind, it is likely that the etiology of carboplatin HSR is multifactorial, involving more than one pathway [9]. Although the mechanisms underlying HSRs are not fully elucidated, many desensitization protocols have been implemented in an attempt to mitigate these reactions. Theprevention of HSRs has been attempted using many premedication regimens [4,5,9,10]. These premedication regimens block the inflammatory pathways involved in HSR. Oral steroids, such as prednisone or dexamethasone have been used to reduce inflammation by achieving capillary membrane stability and suppression of the immune response. Escalating concentrations of antihistamines, like diphenhydramine (H-1 blockers) and famotidine (H-2 blockers), are utilized to help prevent mast cell degranulation [5,10]. Notably, some premedication regimens require an extended 5 days of therapy. These prolonged regimens, in addition to the administration of corticosteroids and antihistamines, have included application of selective leukotriene receptor antagonist (montelukast) and non-steroidal anti-inflammatory inhibitors (indomethacin) [5,10]. These premedication regimens are implemented, along with a slow infusion of increasing carboplatin concentration, to prevent both a type I and type IV hypersensitivity response to carboplatin.

Carboplatin administration in a patient with hypersensitivity can be severe and potentially life-threatening. Therefore, some authors argue to discontinue platinum treatment at the initial sign of a HSR. These same authors suggest exhausting all other options before utilizing a desensitization protocol [2,11,4]. Due to the severity of a carboplatin hypersensitivity, patients must be selected properly to ensure safety during standard carboplatin administration. To determine patient eligibility for a desensitization protocol clinicians use either, 1) clinical evidence of HSRs during carboplatin infusions, or 2) a carboplatin skin test method. In the first group, clinical evidence of hypersensitivity reactions are graded 0 through 5 (grade 5 being death) by using the NCI Common Terminology Criteria for Adverse Events (CTCAE v. 4.03, Table 1). For the second group, there is no clinical evidence of HSRs, therefore, utilizing the skin test method helps to determine patients at risk for developing carboplatin hypersensitivity [12]. Since Zannoti et al.'s index study of carboplatin skin tests, various other authors have reported false-negative rates as high as 8.5% [10,13–16]. To prevent HSR in patients with a positive skin test or history of HSRs, a carboplatin desensitization (CD) protocol can be employed. Desensitization protocols utilize hypersensitivity-mitigating pre-medications like antihistamines and corticosteroids. Following the pre-medication's temporary state of reduced immune reactivity, carboplatin infusion is initiated at increasing concentrations. Windom et al. first successfully described this technique in 1992 [10]. Since then, multiple investigators have reported successful platinum desensitization regimens [9,17–19].

Many previously published carboplatin desensitization protocols are heterogeneous and vary in terms of their safety, speed, location, effectiveness, and validation. The current existing protocols have time intervals that can range from 2 to 16 h, initially take place in an intensive care unit (ICU), require multiple steps, lack effectiveness (60% of patients with reacts during desensitization), apply <6 cycles per patient, and relate only to a restricted number of patients (4 to 57 patients) with mild grade reactions [20–25]. Given this heterogeneity, large retrospective studies or randomized controlled trials exploring carboplatin desensitization are necessary to elucidate the optimal regimen. The purpose of this study is to describe, with the largest retrospective data in the literature, our carboplatin desensitization protocol. This protocol can be used as a means of continuing therapy for patients harboring HSRs and positive skin tests. Additionally, we aim to identify risk factors in patients with adverse events during CD.

2. Materials and methods

An institutional-review board approval was obtained from the Yale Human Investigations Committee (HIC# 1308012505). A retrospective review of the Yale-New Haven Hospital Tumor Registry was conducted. All gynecologic cancer patients who received chemotherapy between 2005 and 2014 were identified. Patients with a history of either a positive carboplatin skin test (administered after 6 cycles of a carboplatin-based chemotherapy regimen), or a history of prior HSRs to carboplatin were selected. Of the patients identified, those who underwent carboplatin desensitization were selected for inclusion. The CD utilized in this study was based on our institutional protocol (Table 2).

Baseline demographic data including age, race, cancer diagnosis, and cancer stage were documented. Details about their desensitization regimens were also collected. Information included, indications for desensitization, location of desensitization, and number of platinum doses received prior to desensitization. Patients with a history of HSRs prior to desensitization had their grade and symptoms recorded. The location, symptoms and grade of HSR during desensitization were documented and reported for all patients undergoing desensitization. Reaction symptoms were graded on a scale from 0 to 5 using the Common Terminology Criteria for Adverse Events (CTCAE v. 4.03, Table 1) [26].

Table 1
Grading system for carboplatin hypersensitivity reactions with the NCI Common Terminology Criteria for Adverse Events (CTCAE v. 4.03).

Grade	Clinical manifestations
0	No reaction
1	Mild: transient flushing/rash, drug fever <38 °C
2	Moderate: rash, flushing, mild bronchospasm
3	Severe: symptomatic bronchospasm ± urticaria, edema/angioedema, hypotension
4	Life-threatening: anaphylaxis
5	Death

Table 2
Yale-New Haven Hospital carboplatin desensitization protocol.

Home Premedications (2 drug regimen):
1. Fexofenadine - 60 mg BID 24 h prior to protocol, 120 mg 3 h prior to protocol
2. Dexamethasone - 20 mg 12 h prior to protocol, 20 mg 3 h prior to protocol
Premedications prior to desensitization protocol (3 drug regimen):
1. Dexamethasone 20 mg IV 30 min prior to protocol
2. Famotidine 20 mg IV 30 min prior to protocol
3. Diphenhydramine 50 mg IV 30 min prior to protocol, 25 mg every 4 h × 3 doses
Carboplatin desensitization protocol
Determine total dose using Calvert equation, estimated or measured CrCl
Bag 1 - 1/1000 dilution in 30 cm^3 NS. Infuse over 30 min
Bag 2 - 1/100 dilution in 50 cm^3 NS. Infuse over 30 min
Bag 3 - 1/10 dilution in 100 cm^3 NS. Infuse over 60 min
Bag 4 - remainder of total dose mixed in 250 cm^3 NS and infused over at least 90 min

Yale-New Haven Hospital carboplatin desensitization protocol. NS (normal saline), min (minutes), CrCl (creatinine clearance).

Please cite this article as: G. Altwerger, et al., Platinum desensitization in patients with carboplatin hypersensitivity: A single-institution retrospective study, Gynecol Oncol (2016), http://dx.doi.org/10.1016/j.ygyno.2016.09.027