Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Review Article

Outpatient desensitization in selected patients with platinum hypersensitivity reactions

David M. O'Malley [a,*], Monica Hagan Vetter [a], David E. Cohn [a], Ambar Khan [b], John L. Hays [c]

[a] Division of Gynecology Oncology, Department of Gynecology and Obstetrics, The Ohio State University College of Medicine, Columbus, OH 43220, USA
[b] Department of Pharmacy, The Ohio State University Comprehensive Cancer Center, Columbus, OH 43220, USA
[c] Division of Medical Oncology, Department of Internal Medicine, The Ohio State University, Columbus, OH, USA

HIGHLIGHTS

- The primary risk factor for platinum hypersensitivity reactions is prior exposure.
- A new classification system for hypersensitivity reactions is proposed.
- A management algorithm for platinum hypersensitivity reactions is discussed.
- Outpatient desensitization of patients with prior reactions is feasible.

ARTICLE INFO

Article history:
Received 6 October 2016
Received in revised form 7 March 2017
Accepted 22 March 2017
Available online xxxx

Keywords:
Carboplatin
Hypersensitivity reactions
Desensitization

ABSTRACT

Platinum-based chemotherapies are a standard treatment for both initial and recurrent gynecologic cancers. Given this widespread use, it is important to be aware of the features of platinum hypersensitivity reactions and the subsequent treatment of these reactions. There is also increasing interest in the development of desensitization protocols to allow patients with a history of platinum hypersensitivity to receive further platinum based therapy. In this review, we describe the management of platinum hypersensitivity reactions and the desensitization protocols utilized at our institution. We also describe the clinical categorizations utilized to triage patients to appropriate desensitization protocols.

Contents

* Corresponding author.
E-mail address: david.o'malley@osumc.edu (D.M. O'Malley).

http://dx.doi.org/10.1016/j.ygyno.2017.03.015
0090-8258/

1. Introduction

Platinum-based chemotherapies are widely used in the treatment of gynecologic malignancies and are a standard treatment option for both initial therapy and recurrent disease. As a result of the widespread use of carboplatin and cisplatin, the management of platinum hypersensitivity reactions (HSR) is an important topic for practitioners in the treatment of gynecologic malignancies. The purpose of this article is to discuss the current classification system of HSR, to discuss clinical features used to triage patients with HSR to appropriate management algorithms, and to describe the management of platinum HSR and subsequent desensitizations with an emphasis on outpatient management strategies.

2. Epidemiology, mechanisms, and risk factors

2.1. Incidence and risk factors for HSR

Carboplatin HSR affect an estimated 5% of the general oncologic population and occur at a rate of approximately 1% of all platinum administrations [1]. Improved survival in ovarian cancer patients has led to patients receiving multiple platinum-based regimens in the recurrent setting thus increasing total exposure to platinums. Additionally, HSR to platinum agents generally develop after multiple cycles of treatment. An incidence of HSR in up to 27% of patients receiving seven or more cycles of carboplatin has been reported [2,3]. This figure approaches the incidence of atopy in the general population which ranges from 19.4–40% [4]. In patients receiving less than five cycles of platinum, the incidence of HSR is reportedly <1%. Platinum HSR are most commonly acute in nature. However, a rare but clinically challenging scenario is a late or "atypical" reaction that manifests after completion of treatment to 14 days following treatment [5]. These reactions are characterized by rash, facial flushing, and/or gastrointestinal symptoms.

Given the potential for life-threatening HSR the identification of factors that increase HSR is important in order to institute preventative measures and be prepared to manage HSR in order to avoid poor outcomes. There have been a number of studies attempting to identify risk factors of HSR. Prior platinum exposure appears to be the primary risk factor for the development of HSR [2,6]. In one study of patients receiving carboplatin for all tumor types, patients who developed HSR had an average total lifetime dose of carboplatin of 3850 mg compared to 1792 mg in the patients who did not develop HSR [2]. A subset analysis of ovarian cancer patients confirmed patients that experienced HSR received an average of 5218 mg of carboplatin over their lifetime compared to non-reacting patients who received 3196 mg. Studies have also shown a correlation between the number of cycles of carboplatin administration and the development of HSR with a significant increase in the occurrence of HSR after seven cycles of treatment [7].

A number of other risks factors have been associated with an increased risk of HSR. In patients with recurrent disease, a longer interval from prior platinum exposure has been associated with an increased risk of HSR. In one study, 25.8% of patients with a platinum-free interval of <12 months had a HSR as opposed to 56.5% of patients with a platinum-free interval > 12 months [8]. A history of prior systemic allergic reactions appears to slightly increase the risk of development of HSR [2,9]. Li et al. reported an incidence of atopy of 44%in patients with HSR to platinum drugs [10], which is slightly higher than the incidence described in the general population. The schedule of administration of the platinum agent has also been associated with increased risk of HSR. In a pediatric population, weekly administration of carboplatin increased the rate of HSR from 2% to 30% [11]. However, the association of the frequency of administration of platinum and the incidence of HSR is less clear in the adult population [12].

A recent report identified deleterious BRCA mutations as an independent risk factor for platinum HSR [13]. In this retrospective study of 87 women receiving carboplatin and olaparib for treatment of ovarian cancer, 93% of patients who developed a HSR had a deleterious BRCA1/2 mutation versus 50% of patients without HSR. Patients with a deleterious BRCA1/2 mutations also had onset of HSR at a lower cumulative exposure compared to patients without a BRCA mutation. The increase in HSR in BRCA mutation carriers was confirmed on multivariate analysis controlling for potential confounding variables with an odds ratio of 13.1 (2.6–65.4; $p = 0.0017$).

Finally, it appears that, when combined with other cytotoxic chemotherapies, the agent given with the platinum impacts the risk of platinum HSR. In the randomized Gynecologic Cancer InterGroup (GCIG) CALYPSO study of carboplatin/paclitaxel (CP) versus carboplatin/pegylated liposomal doxorubicin (CD) in platinum sensitive ovarian cancer, there was a significantly increased risk of HSR in patients treated with CP compared to CD (33% versus 16%, $p < 0.001$) [14]. Nearly half (46%) of the HSR in the CD arm occurred in cycle 1 compared to only 16% of HSR in the CP arm. The GCIG also found that patients >70 years old had significantly lower rates of HSR when treated with CP; however, there was no association with age on the rate of HSR in the CD arm.

2.2. Mechanisms of platinum hypersensitivity reactions

Platinum hypersensitivity reactions were first noted in platinum refinery workers. These reactions, referred to as platinosis, consisted of both respiratory and dermatologic manifestations and ranged from mild to severe [15]. Once workers developed these symptoms, they were always symptomatic in platinum-containing environments; however, it was also noted that patients could be systematically desensitized. It has been postulated that HSR are type I, immunoglobin E (IgE) mediated hypersensitivity reactions [16]. In type I hypersensitivity reactions, IgE bound to mast cells and basophils become activated causing cross-linking of the IgE ultimately resulting in release of pharmacologically active mediators including histamine, leukotrienes and prostaglandins [8]. This is supported by the rapid onset of symptoms during or shortly following carboplatin infusion, positive skin tests in patients who then develop HSR, and the detection of platinum-specific IgE in patients.

More recent research has suggested that there may be a component of Type IV hypersensitivity in platinum HSR. Type IV hypersensitivity reactions are delayed hypersensitivity reactions that are mediated by the release of cytokines from CD4+ helper T cells thereby causing activation of macrophages, neutrophils, or eosinophils [17]. Delayed hypersensitivity reactions tend to present with cutaneous manifestations ranging from mild (eczema or maculopapular eruptions) to life-threatening (bullous or exfoliative reactions including Stevens-Johnson syndrome or acute generalized exanthematous pustulosis). Research performed in metal refinery workers has shown an increase in platinum-salt specific T-cell subpopulations [18]. Furthermore, in vitro stimulation of antigen-presenting cells increased the frequency of specific subpopulation of T cells. This suggests a mixed mechanism involved in HSR which may explain the variation in the presentations of HSR.

2.3. Predicting carboplatin hypersensitivity reactions

Skin testing for prediction of carboplatin HSR was first used in the 1990s [19,20]. Both epicutaneous and intradermal skin testing routes have been investigated and have been used before and after platinum HSR. As the incidence of HSR increases after the seventh cycle of carboplatin administration, most studies initiate skin testing after their sixth cycle [19–22]. The negative predictive value of carboplatin skin testing when performed prior to the development of a HSR ranges from 81 to 92% with a positive predictive value of 86% [19,21]. The rate of HSR in patients who undergo desensitization after having a positive skin test ranges from 14 to 43% [19]. When used after a HSR, the frequency of positive skin tests ranges from 66%–93% [19]. At our institution, we do not routinely utilize skin testing due to the wide range of

Please cite this article as: D.M. O'Malley, et al., Outpatient desensitization in selected patients with platinum hypersensitivity reactions, Gynecol Oncol (2017), http://dx.doi.org/10.1016/j.ygyno.2017.03.015