Platinum Chemotherapy Hypersensitivity

Prevalence and Management

Iris M. Otani, MD[a,*], Johnson Wong, MD[b], Aleena Banerji, MD[b]

KEYWORDS

• Platinum agent • Carboplatin • Cisplatin • Oxaliplatin • Chemotherapy allergy
• Chemotherapy hypersensitivity • Chemotherapy desensitization

KEY POINTS

- Hypersensitivity reactions to platinum agents are common. For carboplatin and cisplatin, the incidence of the first hypersensitivity reaction is typically clustered around the second and third reexposure during the second line of therapy (eighth and ninth courses overall). For oxaliplatin, the first hypersensitivity reactions occurred throughout the treatment course.
- Skin testing is helpful for risk stratification to choose desensitization protocols and assess risk for breakthrough hypersensitivity reactions during the desensitization.
- A risk-stratification protocol using 3 serial skin tests has been shown to be safe and effective in managing patients with a history of hypersensitivity reactions to platinum-based chemotherapeutic agents.
- The most widely accepted desensitization protocols for platinum agents are the 8-step and 12-step (or modified 13-step) protocols.
- With appropriate clinical history and evaluation, patients can receive first-line chemotherapy treatment safely despite a history of hypersensitivity reactions to platinum-based chemotherapeutic agents.

INTRODUCTION

Cancer is a leading cause of death worldwide and although the incidence continues to rise, cancer mortality has declined over the past decade in large part due to more efficacious chemotherapeutic regimens.[1] The ability to use first-line chemotherapeutic

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[a] Department of Medicine, Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, UCSF Medical Center, 400 Parnassus Avenue, Fifth Floor, San Francisco, CA 94143, USA; [b] Department of Medicine, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, USA
* Corresponding author.
E-mail address: iris.otani@ucsf.edu

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agents in the treatment of patients with cancer is critical to good patient outcomes. However, hypersensitivity reactions (HSRs) have emerged as a significant complication to therapy and an increasing incidence of HSRs to first-line chemotherapeutic agents are limiting their use.

As an example, it is well-described that ovarian cancer is the most fatal gynecologic malignancy.[2] The standard treatment approach for newly diagnosed ovarian cancer involves multidisciplinary treatment, including surgical cytoreduction followed by a platinum-based therapy.[3,4] Despite achieving initial complete clinical remission, the vast majority will go on to develop recurrent ovarian cancer.[5] For women with recurrent ovarian cancer, repeat treatment with carboplatin is the treatment of choice. However, carboplatin retreatment in these patients is associated with a high rate of HSRs ranging from 21% to 47%.[6–8] Unfortunately, patients with recurrent ovarian cancer presenting with drug HSRs are frequently and irreversibly labeled as allergic, preventing the use of first-line therapies. The lack of understanding the standard approach to management after an initial HSR leads to suboptimal outcomes, including needless avoidance of first-line chemotherapeutic agents in patients who could tolerate rechallenge without desensitization or intentional rechallenge with a drug that may cause a recurrent and severe HSR. However, there is significant research and experience showing that an accurate clinical history and proper management can improve patient outcomes despite a reported HSR.

This review focuses on HSRs induced by platinum-based chemotherapeutic agents. We review the epidemiology, clinical presentation, and management of HSRs to platinum-based chemotherapeutic agents.

BACKGROUND AND EPIDEMIOLOGY

Carboplatin and cisplatin are platinum-based chemotherapeutic agents commonly used for ovarian, lung, and head and neck cancers. Carboplatin and cisplatin are classified as DNA alkylating agents. Carboplatin was introduced in the late 1980s and has since gained popularity in clinical treatment due to its vastly reduced side effects compared with its parent compound cisplatin. HSRs are rarely reported during the initial treatment and the frequency of HSRs appears directly related to the number of exposures. HSRs are typically noted after multiple cycles have been administered and occur most frequently with the second line of treatment.

With carboplatin, the incidence increases from 1% in individuals who have received 6 or fewer carboplatin infusions to 27% in those who received 7 or more, and up to 46% in patients who have received more than 15 infusions.[6,9] The peak incidence of HSRs occurs with the eighth or ninth exposure, which generally corresponds to the second or third cycle of retreatment after recurrence of malignancy.[9] It is important to note that women with inherited mutations in BRCA 1 or 2 appear to have a higher risk for carboplatin infusion reactions and reactions occur at a lower cumulative exposure.[10,11] Patients with a BRCA 1 or 2 mutation are also at higher risk for reacting during desensitization.[11]

Cisplatin was the first of the platinum drugs to be used but is often limited by side effects, including neurotoxicity, nephrotoxicity, and ototoxicity. These side effects are less common with equal efficacy, making carboplatin a better treatment option for most patients with cancer requiring platinum-based therapy. The incidence of cisplatin hypersensitivity exhibits similar characteristics to those observed with carboplatin. One of the first publications on cisplatin as a treatment for lung cancer described that, among patients receiving 6 or more cycles of combination chemotherapy, 5 of 21 patients experienced “anaphylaxis.”[12] In general, the frequency of