Successful desensitization after hypersensitivity reaction to cisplatin in a patient with nasopharyngeal carcinoma

Arisa Kinouchi[1], Hiroki Ishii[1], Kaname Sakamoto[1], and Daiju Sakurai[1]

[1]University of Yamanashi

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Abstract

Hypersensitivity reaction (HSR) to cisplatin can result in discontinuation of chemoradiotherapy in patients with head and neck squamous cell carcinoma (HNSCC). We present a nasopharyngeal carcinoma patient with cisplatin hypersensitivity successfully treated with cisplatin-desensitization. Desensitization therapy may be safe and beneficial in patients with HNSCC who develop HSR to cisplatin.

1. Introduction

Cisplatin (CDDP) is a well-known platinum-based chemotherapeutic agent. It is the backbone of cancer treatment for various types of cancers, and credible evidence indicates that it is effective for head and neck squamous cell carcinoma (HNSCC). However, repeated exposure to platins, such as CDDP and carboplatin (CBDCA), increases the risk of hypersensitivity reaction (HSR) to platins [1]. HSR to platins critically influences the patient's prognosis. Desensitization therapy has been proposed for patients with gynecological cancer who have the risk of HSR [2]. Although several studies have evaluated the effectiveness and safety of desensitization with platins, few reports have described desensitization to CDDP in patients with HNSCC.

We herein present a case of acceptable re-challenge in a patient with nasopharyngeal cancer who had a history of HSR to CBDCA. The patient underwent a desensitization protocol for HSR to CDDP involving a series of CDDP administrations diluted by 10 times the desired dose. Although a mild urticarial rash occurred during CDDP desensitization therapy, the patient tolerated a cumulative dose of 200 mg/m^2, and no recurrence was detected 1 year after chemoradiotherapy with desensitization.

2. Case Presentation

A 75-year-old Japanese woman presented for evaluation of bilateral neck swelling. She had a medical history of uterine cancer treated by total hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection at 58 years of age, followed by six cycles of adjuvant chemotherapy with CBDCA (area under the blood drug concentration–time curve of 6 mg*h/L) and paclitaxel (180 mg/m^2). Computed tomography and magnetic resonance imaging revealed a neoplastic process in the right fossa of Rosenmuller with invasion of the parapharyngeal space and bilateral enlarged upper-middle internal jugular lymph nodes with necrosis; however, there was no evidence of distant metastatic disease (Figure 1). Pathological examination revealed a non-keratinizing nasopharyngeal carcinoma. The patient was clinically diagnosed with advanced nasopharyngeal carcinoma (cT2N3M0, Stage IVA). She had started chemoradiotherapy using CDDP, which is a scheduled intensity-modulated radiotherapy (70 Gy in 35 fractions), with three cycles of concomitant CDDP (100 mg/m^2) once every 3 weeks. Although no adverse effects occurred during the first cycle of CDDP, the patient developed a feeling of malaise 16 minutes after the start of the second CDDP administration on day 22. She then further developed urticaria on her neck with itching, followed by vomiting, cold skin, and bowel incontinence. Her blood pressure temporarily decreased to 67/43 mmHg, and her oxygen saturation

decreased to 93% on room air. Because these observations suggested a state of shock, a clinical diagnosis of CDDP anaphylaxis was made. The infusion was immediately stopped, and first-line treatments were administered (intramuscular adrenaline, high-flow oxygen, and saline infusion). Intravenous hydrocortisone and chlorophenylamine were also given. The patient appeared to recover, and no additional interventions were needed. Approximately 20 mg of CDDP had been administered during the infusion.

HSR to CDDP was strongly suspected. Because there were no alternative treatments as effective as the current treatment using CDDP to control the targeted lesions, CDDP desensitization therapy was performed with the approval of our institution's ethics committee. This desensitization protocol involved four different solutions of 1/1000-, 1/100-, and 1/10-diluted CDDP as well as the original concentration. First, 500 mL of normal saline containing the target dose (140 mg) of CDDP was first processed as the original solution. Next, this original concentration was diluted 10 (solution #3), 100 (solution #2), or 1000 times (solution #1) by saline. After the patient had been premedicated with an H1 antagonist (chlorpheniramine), H2 antagonist (famotidine, 20 mg), and glucocorticoid (dexamethasone, 6.6 mg), these processed solutions were administered in the order of lowest to highest CDDP concentration.

Desensitization therapy started 14 days after the development of HSR to CDDP. The timeline of desensitization is shown in Figure 2. The infusion of solutions #1 and #2 was smoothly completed with no allergic reactions indicating hypersensitivity to CDDP. However, after the scheduled administration of solution #3 at a 1-hour interval, grade 1 redness and itching of about 30 mm in diameter appeared at the injection site. To allow for continuation of the desensitization with the original solution, clobetasol propionate ointment 0.05% was applied to the injection site. Although the infusion rate of the original solution was decreased from 160 to 120 mL/h, grade 1 urticaria broadly spread to the patient's face and neck with dry coughing 1 hour after starting desensitization (Figure 3). We reduced the infusion rate to 90 mL/h in a stepwise manner; however, the urticaria continued spreading to her abdomen and lower legs 2.5 hours after the start of desensitization with solution #4 (grade 2). She was administered 100 mg of hydrocortisone, and all symptoms resolved within 30 minutes. Finally, a target dose of CDDP was administered successfully with no further reactions.

The patient completed radiotherapy (total dose of 70 Gy in 35 fractions) and was discharged 2 weeks after the scheduled CDDP desensitization therapy. Computed tomography revealed significant therapeutic responses at both the primary site and bilateral neck lymph nodes at 3 months post-desensitization (Figure 4). A complete response was achieved. At the time of this writing, the patient had been alive and well without disease for 1 year.

3. Discussion

CDDP commonly causes emesis, myelotoxicity, nephrotoxicity, and ototoxicity [3]. Incidentally, some patients develop HSR to CDDP [4]. The mechanism of HSR to platins is unclear but is considered to be an immune reaction that occurs via immunoglobulin E-mediated activation of mast cells and their rapid degranulation with the release of histamine [5].

Symptoms of mild HSR include skin rash, urticaria, flushing, palmar itching, burning, edema of the face and hands, abdominal cramping and diarrhea, back pain, and pruritus. Severe HSR can be life-threatening if the patient develops severe hypotension, bronchospasm, cardiac dysfunction, or anaphylaxis [6]. Repeated exposure to platins directly increases the risk of HSR, and HSR often occurs after administration of multiple cycles [7]. In patients receiving CBDCA, a platinum-free interval of >12 months and cumulative dose of >650 mg are associated with the incidence of HSR [8,9]. The frequency of HSR to CDDP ranges from 5% to 20% and increases with concomitant radiation therapy in patients with gynecologic cancers, but the incidence of HSR in patients with head and neck cancers is unknown because it rarely occurs [10]. In this case, the patient had received a cumulative CBDCA dose of 3,900 mg, and her sensitization to platins may have progressed over time. This may be explained by the cross-reactivity among platinum agents. The cross-reactivity between CDDP and CBDCA can be explained by the similarity of their structure. The central core of all platins is a platinum atom coordinated with two nitrogens. The structure of two primary amine chains (NH_3), which is shared by CBDCA and CDDP, could be due to the cross-reactivity between these

two drugs [11]. Thus, our patient may have developed HSR to CDDP after multiple exposures to CBDCA. Because there is little evidence of HSR to platins in patients with head and neck cancers, we were unable to anticipate the risk of HSR before initiation of our patient's treatment. Before administering platinum-based chemotherapy, skin testing can be performed to evaluate the risk of HSR in patients with a history of platinum administrations [12]. Pradelli et al. [13] reported that the negative predictive value for skin testing was 92% for all platins, 100% for CDDP, and 87% for CBDCA. However, we were unable to perform skin testing before CDDP desensitization therapy because it was not covered by insurance in Japan.

Several desensitization protocols for CDDP or CBDCA in patients with gynecologic cancer have been described. Many previously reported protocols involve 12 steps using 3 dilutions (1:100, 1:10, and 1:1) by increasing the infusion rate; however, such protocols are complicated [10]. Therefore, with reference to a previous report by Takase et al. [14], we performed a desensitization protocol with four different solutions (1/1000-, 1/100-, and 1/10-diluted CDDP as well as undiluted CDDP). We adopted this protocol because of its simplicity and rapidity. Takase et al. [14] reported that the completion rate of this protocol was 95.2% in a group of 20 patients, among whom only 1 developed grade 3 HSR. Their result encouraged us to use this protocol with effectiveness and safety.

Conclusion

We have reported a case of successful desensitization therapy in a patient with HNSCC who developed HSR to CDDP. Although HSR to platins rarely occurs in patients with HNSCC, it can occur whenever there is re-exposure to platins. Furthermore, a CDDP desensitization protocol using a series of CDDP administrations diluted by 10 times the desired dose was clinically acceptable and safe. However, because of the limited number of reports of HSR to platins in patients with HNSCC, further studies are warranted to overcome platinum hypersensitivity and safely administer desensitization protocols to these patients.

References

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Figure legend

Figure 1: CT scan images before chemoradiotherapy.

(A) An enhancing soft-tissue lesion located in the right wall of the nasopharynx (red arrow). (B-C) Gadolinium-enhanced T1-weighted MRI showing the tumor invasion into the parapharyngeal space (B) and multiple enlarged lymph nodes with necrosis in bilateral upper-middle neck (C). The arrow indicates the tumor area.

Figure 2: Timeline and duration of the CDDP-desensitization treatment.

Figure 3: Clinical photographs demonstrating hypersensitivity reactions during CDDP-desensitization.

(A) Pruritus appeared around the injection area. (B) Redness on the face.

Figure 4: CT scan images on 3 months after chemoradiotherapy.

(A-B) The enhancing lesions in the right nasopharynx (A) and multiple enlarged bilateral cervical lymph nodes (B) have disappeared.

Figure 1

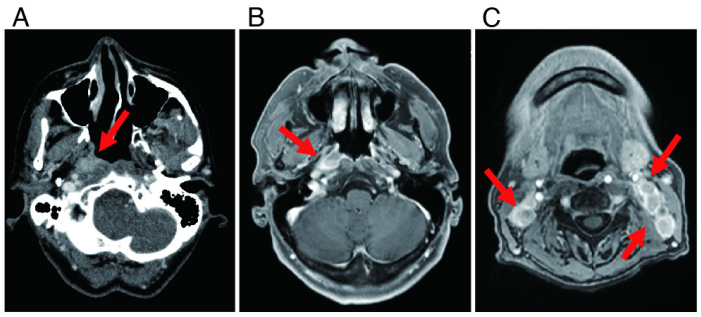

Figure 2

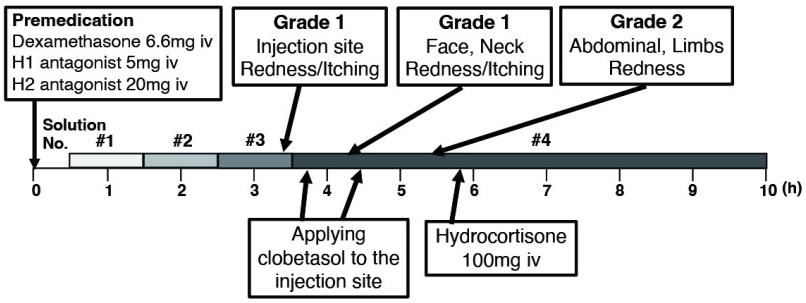

Figure 3

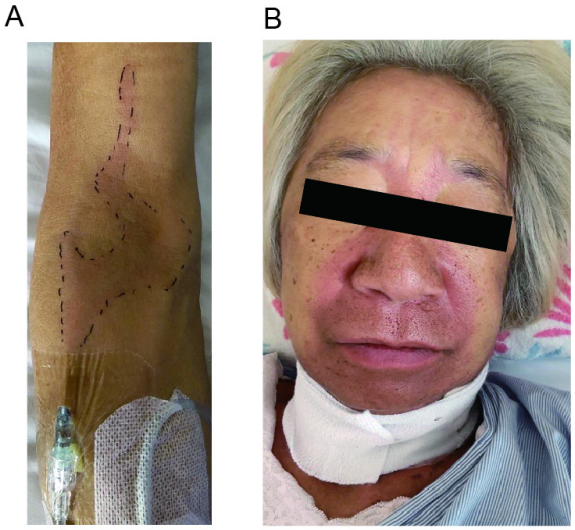

Figure 4