Introduction

Carboplatin is widely used in gynecological cancers, and a combination chemotherapy with paclitaxel (TC) is applied as first-line chemotherapy for ovarian and uterine cancers. TC therapy is also used in platinum-sensitive recurrent gynecologic cancer. Carboplatin has a known hypersensitivity reaction (HSR) to repeated drug exposure. HSR to carboplatin occurs in cases with repeated administration, and the number of cycles of carboplatin administration is an important risk factor in its development. The incidence of HSR is 0.9% before the 6th infusion, then increases to 6.5% in the 6th, 7.0% in the 7th, and to a peak of 19.5% in the 8th infusion. At more than the 9th infusion, the incidence is around 10% [1].

Because 6 cycles of TC therapy are commonly administered for first-line chemotherapy in advanced gynecologic malignancies, HSR to carboplatin is likely to occur in second-line chemotherapy for recurrence. There are various symptoms of HSR, including tachycardia, alterations in blood pressure, dyspnea, shock vital, flushing, chest pain, back pain, fever, itching, nausea, and rash [2]. Although the incidence of severe reactions is less than 5%, death can occur in the worst case. Desensitization to carboplatin is effec-

Hypersensitivity Reaction to Carboplatin in Gynecologic Cancer: A Case Report and a Review of the Literature

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Abstract: A combination chemotherapy of paclitaxel plus carboplatin (TC) is the most frequently used regimen for gynecological malignancies. As long as it is effective, a carboplatin-containing combination chemotherapy is used for every relapse. This implies that the number of platinum administrations and the frequency of hypersensitivity reaction (HSR) increase as the prognosis improves. When a patient develops HSR to carboplatin, we have three options: 1) desensitizing and continuing to use carboplatin, 2) switching to other platinum drugs, or 3) changing to a non-platinum drug. Here we report an experience of an HSR to carboplatin in a patient with recurrent uterine carcinosarcoma. The patient was treated by surgery and TC therapy initially, resulting in no residual disease. The patient relapsed 18 months after the completion of the first-line chemotherapy and was treated with TC therapy again as second-line. An HSR to carboplatin occurred at the 10th cycle of TC in total. We replaced the carboplatin with cisplatin. A chemotherapy including cisplatin and adriamycin was repeated without further HSR. We reviewed the literature regarding HSR to carboplatin and in this paper we summarize the management for dealing with it.

Keywords: hypersensitivity reaction, carboplatin, cisplatin, chemotherapy, uterine carcinosarcoma.

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tive, and shifting other platinum agents, e.g. cisplatin, is also reported. Changing to non-platinum agents is not a high precedent for prolonged prognosis [3].

Here we report a case with recurrent uterine carcinosarcoma who showed HSR to carboplatin in the 10th cycle of TC therapy. After HSR, we switched from carboplatin to cisplatin. The patient was treated with a combination chemotherapy of adriamycin and cisplatin, and the recurrent disease was well controlled without further HSR. In this report, we also summarize previous reports describing HSR in which carboplatin was switched to cisplatin.

**Case**

A 60-year-old woman, gravida 2, para 2, was referred to our hospital by a local gynecologist for uncontrolled genital bleeding after cervical biopsy. The patient had a gross tumor in the endocervix. A computed tomography (CT) scan revealed a mass of 65 × 58 × 56 mm in the uterine cervix, with papillary prominence in the endometrium and fluid accumulation in the uterine cavity. Enlarged metastatic lymph nodes were observed around the bilateral internal and external iliac arteries. The tumor was considered as cervical adenocarcinoma, FIGO stage IIB at first, based on both the CT scan and clinical evaluation. Radical hysterectomy, bilateral salpingo-oophorectomy, pelvic lymph node dissection, and para-aortic lymph node biopsy was performed as the initial treatment. The post-operative histological diagnosis was carcinosarcoma, heterologous type including endometrial adenocarcinoma, rhabdomyosarcoma, and an osteosarcoma component of the uterine corpus, FIGO stage IIIC, pT2N2M0.

On the 15th postoperative day, TC (carboplatin AUC5 and paclitaxel 180 mg/m²) combination chemotherapy was administered as adjuvant therapy for carcinosarcoma of the uterine corpus. Paclitaxel was administered for over three hours during the TC chemotherapy, after which carboplatin was administered. The patient had received routine antiemetic mediation with intravenous dexamethasone 16.5 mg, palonosetron 0.75 mg, chlorpheniramine Maleate 5 mg, and famotidine 20 mg, 30 min prior to the infusion. The treatment was planned to six cycles, every three weeks, and was completed as scheduled without severe complications.

After completion of the initial therapy, the patient was monitored every 1–3 months. At 18 months from the completion of TC therapy, a CT scan revealed intraperitoneal disease recurrence with multiple lymph node metastases. Because it had been 18 months since the end of the first treatment, we decided to treat the patient with TC therapy again.

During the 4th cycle of TC therapy for recurrence (the 10th cycle in total), the patient had flush and heat on the face and upper extremities at 30 minutes after the administration of carboplatin. Her condition was diagnosed to be a grade 2 (CTCAE v4.0) HSR, and the TC was discontinued. We administered d-chlorpheniramine maleate, which improved her symptoms. We explained three options to her for continued treatment: 1) desensitizing and continuing to use carboplatin, 2) switching to other platinum drugs, or 3) changing to a non-platinum drug. After obtaining informed consent, we determined to substitute cisplatin for carboplatin to continue the platinum-based combination therapy. The patient received AP (adriamycin 60 mg/m², cisplatin 50 mg/m²) therapy after 3 weeks after the HSR. A CT scan showed a partial response after 3 cycles of AP therapy, but she had to discontinue chemotherapy due to fatigue and prostration caused by a lumbar compression fracture after 4 cycles of AP therapy, at which time partial response to AP therapy was confirmed by a CT scan. The patient presented with disease progression at 2 months after the last cycle of AP therapy and was thereafter given radiation therapy as palliative therapy.

**Discussion**

We experienced HSR to carboplatin during the 10th TC therapy in a patient with recurrent uterine carcinosarcoma. Since AP therapy has been shown to be an effective treatment for uterine carcinosarcoma [5], we chose to switch to cisplatin rather than to continue carboplatin through desensitization. Cisplatin had been used as the standard treatment for ovarian cancer before carboplatin was used. According to a phase III study for first line chemotherapy of ovarian cancer reported in 2003, carboplatin was replaced with cisplatin due to its favorable nephroxicity and neurotoxicity.
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As cisplatin’s effectiveness and side effects are well recognized by gynecologists, switching from carboplatin to cisplatin is a reasonable option for cases in which continuation of platinum-based chemotherapy is favorable.

Paclitaxel can also cause HSR in 9% of TC therapy administered for gynecologic cancers. Paclitaxel-induced HSR can be prevented by premedication and can be re-administered [7].

On the other hand, carboplatin-induced HSR can not be suppressed with premedication. Dizon et al, for example, reported that severe HSR occurred in 2 of 7 cases, even when pretreatment with cimetidine, dexamethasone, and diphenhydramine was used [8]. Therefore, carboplatin-induced HSR requires switching to other platinum agents or carboplatin desensitization therapy. For platinum-sensitive recurrent cancer, conversion to non-platinum drugs should be avoided because it’s unclear whether it will have the same effect as platinum in the patient [3]. Carboplatin-induced HSR is caused by IgE-mediated release of histamine, leukotrienes, prostaglandins, etc. as a type I allergy or immediate hypersensitivity when the constituents of an anticancer drug are recognized as antigens. Instant response caused by IgE develops within sixty minutes of carboplatin administration [4]. It is important to discriminate carboplatin-induced HSR from other allergic reactions, including paclitaxel-induced HSR. Banerji et al reported that paclitaxel-induced HSR often included symptoms of face flushing, back pain, and chest or throat tightness. In contrast, patients with an HSR reaction to carboplatin more frequently presented with symptoms of itchy palms and feet, general urticaria, and/or erythema, vomiting, hypotension, and coryzal symptoms [9]. In our case, we could distinguish these HSRs based on the symptoms and the timing of onset.

There is no significant difference in HSR among the types of cancer in severity, symptoms and the rate of occurrence, but in the case of gynecologic cancer, TC therapy is selected as both first-line chemotherapy and second-line chemotherapy. Therefore, the total dosage and the number of administration cycles tend to increase compared to other cancers. As a result, HSR is a characteristic of patients with recurrent gynecological cancer who receive platinum-based chemotherapy. In addition to the increased number of exposures, younger age has been suggested as a risk factor for carboplatin-induced HSR. For example, high frequencies of carboplatin-induced HSRs have been reported in pediatric glioma in children: 40% in a Turkish study [10] and 42% in a Canadian study [11]. In another report, Joly et al analyzed a large cohort of patients with relapsed ovarian cancer in which older patients (>70-year-old) had lower rates of HSR to carboplatin [12]. Presumably, a decline in immune function in the elderly women had less treatment-induced allergy. Our case was as young as 60 years old, which may have been a factor in the HSR.

Desensitization therapy in combination with platinum drugs has been shown to be more effective than treatment with non-platinum-based monotherapy after the onset of HSR. Desensitization therapy with carboplatin requires adjustment of the solution and the method of administration [13]. One of the methods is to start with very low concentrations of the drug over 24 to 48 hours. The other is to divide the concentration into 5 to 13 levels and after that to raise the level gradually over a period of 5-8 hours. Because it is very complicated, it is generally done in the hospital but not in an outpatient setting. As a simple desensitization therapy, it is reported to be safe and effective to make 4-step dilutions of carboplatin (undiluted, 1/10, 1/100, and 1/1000), administering the lowest concentration of carboplatin over an hour or more in the order in which it is administered. However, there is a variety of challenges in desensitization therapy, including the need to clearly rule out HSR due to the diversity of HSR symptoms and determining the criteria for when to re-administer it. In addition, the drug cannot be continued if a grade 3 or higher adverse event occurs or if the patient is refractory to treatment [14, 15].

Switching from carboplatin to cisplatin could be a reasonable option. The carboplatin desensitization described above needs to be done in every chemotherapy, taking more than 4-hours, while desensitization is not necessary in the case of switching to cisplatin [16]. In this approach, therefore, platinum-based therapy can be continued basically without desensitization or the use of long premedication regimens. In fact, our case did not receive any desensitization step after HSR to carboplatin and was able to continue platinum-based therapy.
chemotherapy, AP therapy, with more than 5 months of progression free-survival time. However, switching should be used with caution in grade 3 or higher HSR cases for safety reasons.

We summarize reported cases of switching to cisplatin from carboplatin due to HSR (Table 1). In 2003, Ottaiano et al reported 10 patients presenting with moderate/severe hypersensitivity reactions to carboplatin. They replaced carboplatin with cisplatin and continued platinum-based chemotherapy. Only 1 patient showed a mild allergic reaction of urticaria, after one cycle of cisplatin [17]. Favorable results were also reported by Kandel et al, where cisplatin replacement was performed in five patients without any hypersensitivity [18]. On the other hand, because 1 of 7 cases resulted in HSR-caused death, Dizon et al did not recommend routine replacement with cisplatin in the relapsed setting without careful consideration of potential risks and benefits [8]. In another report of 24 patients with HSR to carboplatin, 18 patients (75%) tolerated cisplatin without any adverse events [16]. In a recent report by Bergamini et al, 37 patients with a previous HSR to carboplatin were treated with cisplatin; of these, 5 patients experienced mild HSR to cisplatin [19]. Notably, all of the above cases did not receive desensitization. The doses of cisplatin varied between reports, and there is no clear criteria for the dosage.

In summary, more than 70% of patients were able to receive platinum without repeated HSR. Although the observed HSR after switching were mostly mild, severe side effects and death could occur. Although most reports described that switching from carboplatin to cisplatin is safe in the situation in which patients can be treated immediately in the event of severe hypersensitivity, some reports have raised the risk of death after switching. Therefore, when making the decision after HSR, a careful consideration of the potential risks and benefits is necessary.

The frequency of HSRs varies depending on the anticancer drugs combined with carboplatin. Clinical trials have shown that the incidence of HSRs is reduced when carboplatin is combined with liposomal doxorubicin (PLD-C). For platinum-sensitive recurrent ovarian cancer, 976 patients were analyzed in a phase III trial, with toxicity data available for 466 and 502 on the PLD-C and TC arms, respectively. There was a 15.5% HSR rate associated with PLD-C vs. 33.1% with TC [12]. Suppressive effect on HSR to carboplatin by PLD-C combination therapy was also confirmed by a Japanese randomized prospective study by Fujiwara et al, in which HSR was observed at 2.0% in PLD-C vs. 13.7% in gemcitabine plus carboplatin [20]. A retrospective study by Shimada et al, in which total of 414 patients (48: PLD-C group, 366: non-PLD-C group) were analyzed, found a 2.1% rate of HSR in a PLD-C group vs. 9.0% in a non-PLD-C group [21]. Based on these results, PLD-C may be a reasonable option for second-line chemotherapy continuing platinum combination chemotherapy while suppressing the frequency of HSR in the treatment of recurrent ovarian cancer.

Conclusions

We experienced an HSR to carboplatin in which switching to cisplatin was effective, showing no fur-
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ther HSR. Our case and previous reports showed that even if HSR to carboplatin occurs, cisplatin can be a safe and useful treatment choice, as long as it is used cautiously and with appropriate assessment of the risk of cisplatin hypersensitivity reactions, taking into account platinum sensitivity.

Conflicts of Interest

The authors declare that there is no conflict of interest.

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