INTERNAL MEDICINE

□ CASE REPORT □

Alert Regarding Cisplatin-induced Severe Adverse Events in Cancer Patients with Xeroderma Pigmentosum

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Abstract

Xeroderma pigmentosum (XP) is a genetic disease in which DNA repair mechanisms are impaired. Cisplatin (CDDP) exerts cytotoxic effects by forming mainly intrastrand DNA cross-links, and sensitivity to CDDP depends on the DNA repair system. Several *in vitro* studies have suggested that treatment with CDDP may cause enhanced adverse events as well as anti-tumor activity in cancer patients with XP. This article is the first to describe two cancer patients with XP showing severe adverse events following CDDP-based chemotherapy. Physicians should pay attention when administering CDDP in cancer patients with XP.

Key words: CDDP, xeroderma pigmentosum, DNA repair system, multiple organ failure

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Introduction

Xeroderma pigmentosum (XP) is a genetic disorder that is associated with an increased incidence of ultraviolet radiation-induced skin cancer (1). XP variant is a subtype of XP involving mutations in the *POLH* gene encoding DNA polymerase η. DNA polymerase η is involved in the translesion DNA synthesis (TLS) pathway, which bypasses damaged DNA and repairs DNA in an error-free or error-prone manner (1, 2). In contrast, the other subtypes of XP involve a genetic defect in the nucleotide excision repair (NER) pathway, which removes damaged DNA from the genome and replicates DNA (1, 3).

Cisplatin (CDDP) is a widely used chemotherapeutic agent that exerts cytotoxic effects by forming mainly intrastrand cross-linked DNA adducts, which block DNA replication and induce apoptosis (4). Resistance to CDDP is, at least in part, associated with the NER and TLS pathways (5-7). Several *in vitro* studies have suggested that treatment with CDDP may cause enhanced adverse events as well as anti-tumor activity in cancer patients with XP. To the best of our knowledge, however, there has been no clinical report regarding the effects of CDDP on cancer or normal cells in patients with XP. We herein report for the first time two cancer patients with XP variant that experienced severe adverse events with multiple organ failure following CDDP-based chemotherapy.

Case Reports

Case 1

A woman in her 70s with a medical history of an XP variant was referred to us for investigation of a nodule that was seen on chest radiography. The diagnosis of XP variant had been made based on the clinical features and a genetic test approximately 20 years ago at a university hospital. The patient had shown weak photosensitivity and undergone surgical resection more than 10 times for repeated skin cancers, but not chemotherapy. She had a family history of a relative with XP and esophageal cancer. On a physical examination, irregular dark spots on the skin were seen all over the body. Chest computed tomography (CT) showed a 2-cm solid nodule in the apical segment (S6) of the right lower lobe. Bronchoscopic examinations pathologically revealed atypical cells in the nodule, and ^{18}F-fluorodeoxyglucose positron emission tomography with integrated CT showed only the lung nod-

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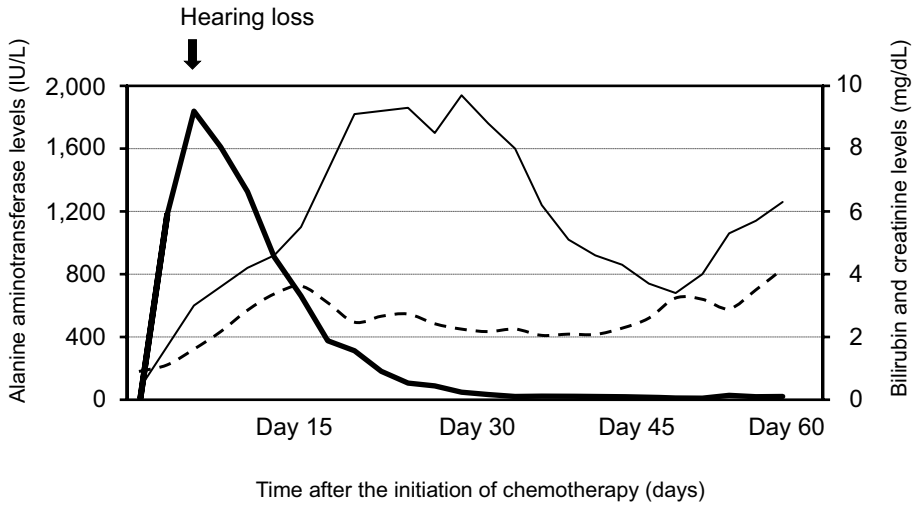

Figure 1. The time course of major adverse events in the lung cancer patient with xeroderma pigmentosum after receiving adjuvant chemotherapy: cisplatin at 80 mg/m^2 and vinorelbine at 25 mg/m^2 on day 1. Bold line: alanine aminotransferase (ALT) levels, thin line: total bilirubin levels, broken line: creatinine levels.

ule with high uptake of ^{18}F-fluorodeoxyglucose. Since the nodule was strongly suspected of being lung cancer, the patient underwent right lower lobe resection. Pathological examinations revealed the tumor, measuring 23 mm in diameter, to be papillary-predominant adenocarcinoma. Although no tumor cells were seen in the hilar lymph nodes, single-station metastasis to the subcarinal lymph node (#7) was observed. The patient was diagnosed with stage IIIA lung adenocarcinoma (pT1bN2M0).

The patient received adjuvant chemotherapy one month after the operation. A combination of CDDP at 80 mg/m^2 and vinorelbine at 25 mg/m^2 was administered on the first day of adjuvant chemotherapy. Fig. 1 shows the time course of the major adverse events experienced following chemotherapy. On the second day, the patient complained of grade 1 diarrhea and grade 2 vomiting according to the Common Terminology Criteria for Adverse Events, version 4.0. On the third day, blood tests revealed grade 4 liver enzyme elevation (alanine aminotransferase [ALT] level: 1,179 IU/L), grade 2 bilirubin elevation (1.7 mg/dL), and grade 2 creatinine elevation (1.11 mg/dL). On the 5th day, the patient suffered from a grade 3 hearing impairment, leading to grade a 4 complete loss of hearing ability. On the 8th day, the acute kidney injury progressed to grade 4 (creatinine level: 3.62 mg/dL), and intermittent hemodialysis was performed. Myelosuppression was also observed, and recombinant human granulocyte colony-stimulating factor was administered to prevent febrile neutropenia. The nadir of the neutrophil and platelet counts was 1,630/μL (grade 1) on the 14th day and 19,000/μL (grade 4) on the 10th day, respectively. A systemic survey including CT of the brain, chest, and abdomen showed no recurrence of lung cancer. Irrespective of intensive treatment, multiple organ failure and systemic infection progressed, and the patient died on the 59th day after the initiation of chemotherapy.

Case 2

During the above-described clinical course, the family members of the first patient reported that similar severe adverse events had been seen in a male relative in his 70s with XP who received chemotherapy for esophageal cancer in another hospital. The relative had been clinically diagnosed with a possible XP variant because of the family history, strong photosensitivity leading to burn-like rashes since childhood, and irregular dark spots of the skin all over the body. With the approval of the family members, his medical information was obtained from the hospital in order to utilize the information for treatment of the first patient. On reviewing his chart, upper gastrointestinal endoscopy at a medical checkup had revealed an ulcerative and localized type of squamous cell carcinoma in the lower portion of the esophagus. The relative had then received subtotal esophagectomy with gastric tube reconstruction for esophageal cancer. Histologically, the tumor, measuring 2.4 cm, had invaded the submucosal layer of the esophagus. The relative had been diagnosed with stage IIB basaloid-squamous cell carcinoma (pT1bN1M0).

Adjuvant chemotherapy had been performed one and a half months after operation. The relative had been scheduled to receive CDDP at 80 mg/m^2 on the first day and 5-fluorouracil at 800 mg/m^2/day as a continuous infusion on the first day through the fifth day. Diarrhea, nausea, and hearing impairment unexpectedly developed on the third day, and the infusion of 5-fluorouracil was discontinued on the 4th day. The time course of the major adverse events experienced following chemotherapy is shown in Fig. 2. The hearing impairment resulted in the use of a hearing aid (grade 3). Liver dysfunction (grade 4 ALT level: 1,009 IU/L; grade 3 bilirubin level: 3.6 mg/dL) and acute kidney injury (grade 4 creatinine level: 6.8 mg/dL) progressed on the 6th

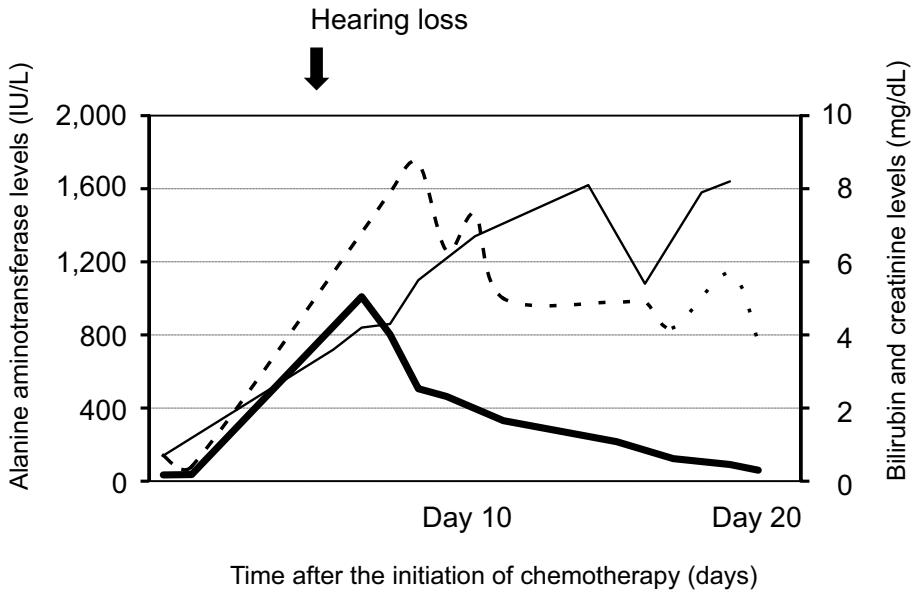

Figure 2. **The time course of major adverse events in the esophageal cancer patient with xeroderma pigmentosum after receiving adjuvant chemotherapy: cisplatin at 80 mg/m^2 on day 1 and 5-fluorouracil continuous infusion at 800 mg/m^2/day on day 1 through day 3. The infusion of 5-fluouracil was discontinued on day 4. Bold line: alanine aminotransferase (ALT) levels, thin line: total bilirubin levels; broken line: creatinine levels.**

day, and hemodialysis was performed. Thereafter, myelosuppression was observed, and platelet transfusion and recombinant human granulocyte colony-stimulating factor were administered. The nadir of the neutrophil and platelet counts was 20/μL (grade 4) and 5,000/μL (grade 4) on the 18th day, respectively. Despite intensive treatment, multiple organ failure progressed, and the relative died on the 21st day after the initiation of chemotherapy.

Discussion

In Japan, the prevalence of XP is 1 in 22,000 individuals, showing that it is not necessarily a rare disease (8). The major subtypes of XP include XP group A, which involves a defect in the XPA protein of the NER pathway, and XP variant, which involves a defect in DNA polymerase η of the TLS pathway (8). Although impairment of the NER and TLS pathways leads to the inability to repair ultraviolet radiation-induced DNA damage, patients with XP variant show mild photosensitivity and a moderately increased risk of developing skin cancer compared to those with XP group A (1, 8). Since the NER and TLS pathways also repair DNA damage induced by chemotherapeutic agents such as CDDP, the effects of DNA-damaging agents on cancer and normal cells may be different between patients with and without XP. To the best of our knowledge, however, there has been no clinical report or any guideline regarding the usage of DNA-damaging agents in cancer patients with XP.

Several *in vitro* studies have shown that defective XPA protein and DNA polymerase η reduce the proliferation and viability of cancer and normal cells. Lung cancer A549 cells transfected with *XPA* antisense RNA show a reduction in cell viability after CDDP treatment (6). Ovarian cancer cells with small interfering RNA-induced knockdown of *POLH* encoding DNA polymerase η exhibit high sensitivity to CDDP (5). In contrast, XPA-deficient GM04312 fibroblasts derived from a patient with XP group A showed moderate sensitivity to CDDP. Additionally, DNA polymerase η-deficient XP30RO fibroblasts from a patient with XP variant were highly sensitive to CDDP (7). These *in vitro* findings suggest that CDDP treatment may have enhanced cytotoxic effects on normal cells as well as cancer cells in patients with XP.

In the present cases, we were unable to completely exclude the possibility that unknown mechanisms, aside from the impairment of DNA repair systems, may exist. For example, DNA polymerase η-deficient GM13154 and GM13155 cells derive from the same patient with XP variant; the GM13154 and GM13155 cells originate from B-lymphocytes and fibroblasts, respectively. While the GM 13154 cells are more sensitive to CDDP, the GM13155 cells are less sensitive (9). Factors other than the loss of DNA polymerase η activity may account for the difference in cytotoxicity of CDDP.

There remains a possibility that vinorelbine and 5-fluorouracil might have induced severe adverse events in these two patients. Both patients shared certain characteristics of severe adverse events: rapid ototoxicity followed by acute kidney injury that needed hemodialysis within one week after chemotherapy. Among chemotherapeutic agents, ototoxicity is characteristic of platinum-containing agents such as CDDP (10). Several randomized studies have shown

that all grades and grade 3 or worse ototoxicity are seen in 18% and 4% of patients treated with single-agent CDDP, respectively (11). In contrast, all grades and grade 3 or worse ototoxicity are observed in 1% and 0% of those treated with single-agent vinorelbine, respectively (12). The combination of vinorelbine with CDDP does not increase the frequency and severity of ototoxicity compared with those treated with single-agent CDDP (11). There has been no report of ototoxicity with 5-fluorouracil. Furthermore, acute kidney injury is a dose-limiting toxicity of CDDP that needs a large quantity of fluid replacement for prevention, whereas acute kidney injury is rarely observed in the treatment with vinorelbine or 5-fluorouracil. In general, vinorelbine interferes with microtubule assembly. 5-fluorouracil is an analogue of uracil, and the metabolites inhibit the synthesis of DNA and RNA. The cytotoxic mechanisms of vinorelbine and 5-fluorouracil are not directly associated with DNA repair systems. Based on these findings, the severe adverse events in the present cases probably resulted from CDDP.

An additional limitation of our report is that a genetic test was not performed in the second patient. The diagnosis of XP is usually based on the clinical findings, family history, and genetic tests; however, there are no established diagnostic criteria for XP (13). Recently, the diagnostic criteria for XP were reported by the Research Committees of the Ministry of Health, Labor of Japan and the Japanese Dermatology Association (8). In brief, a definite diagnosis of XP is established when typical skin manifestations or a family history of XP is present along with a positive genetic test. When a genetic test is not performed, a probable diagnosis requires all of the following: acute photosensitivity, freckle-like pigmentation, and early-onset skin malignancies. A possible diagnosis is given when a patient shows both acute photosensitivity and freckle-like pigmentation. Other diseases with photosensitivity, such as erythropoietic protoporphilia, must be ruled out. Patients with XP do not always show distinctive skin manifestations, and early protection from the sunlight decreases the appearance of skin lesions. The genetic tests are becoming increasingly important for the diagnosis of XP and the management of patients.

Before cancer treatment is started, a genetic diagnosis of XP should be made in patients with clinical findings suggestive of XP. By not selecting CDDP-based chemotherapy, patients with XP may avoid severe adverse events. However, CDDP is a pivotal chemotherapeutic agent in a variety of malignancies. As such, by not selecting CDDP-based chemotherapy, patients with XP may lose an opportunity for long-term survival or achieving a cure. Whether or not cancer patients with XP should receive CDDP-based chemotherapy is a major controversial issue. Our experience with two patients encourages further studies to clarify the association between the underlying biology in XP and the effects of CDDP, which may help in the management of cancer patients with XP.

The results of *in vitro* studies suggest that the adverse effects caused by CDDP on normal cells is, at least in part, protected by DNA repair systems. XP is known to involve the impairment of DNA repair systems. Physicians should therefore be aware that CDDP can potentially induce severe adverse events in patients with XP.

The authors state that they have no Conflict of Interest (COI).

A consent was obtained from the patients' family representative for the publication of this case report.

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