Case Report

Pregabalin Attenuates Carboplatin-Induced Akathisia-Like Neuropathy: A Novel Case Report

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Keywords

Chemotherapy-induced peripheral neuropathy · Akathisia · Restless legs syndrome · Pregabalin · Carboplatin

Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most serious adverse effects of chemotherapy. We experienced carboplatin (CBDCA)-induced akathisia-like CIPN, which was significantly attenuated by pregabalin administration, and report its treatment. A man in his 40s was administered CBDCA + pemetrexed (PEM) as the third-line treatment for recurrent malignant pleural mesothelioma. He rarely experienced mild akathisia-like symptoms on his feet before the diagnosis. The patient claimed that he exhibited mild degradation of the symptoms in the previous cisplatin (CDDP) + PEM treatment without the need for pharmacotherapy. Symptoms notably worsened approximately 7 days after the first cycle of CBDCA + PEM and did not disappear. Furthermore, symptoms worsened during the daytime and became milder at night. Lorazepam (0.5 mg) was administered 3 times a day from day 14 but was not effective. Finally, we evaluated the symptoms to be derived from CBDCA-induced neuropathy as he experienced the same symptoms in CDDP + PEM and did not have suspicious pathology or medicines for akathisia development. We decided to administer 75 mg pregabalin twice daily, resulting in significant symptom improvement. He also complained that he felt the symptoms 10 h after the previous pregabalin dose, suggesting that pregabalin was effective, and its effect weakened or disappeared as time progressed. Akathisia-like symptoms caused by CBDCA-induced CIPN are rare, but they significantly reduce the quality of life. Pregabalin was significantly effective in this case; therefore, we suggest that a detailed symptom interview and selection of the medicine, based upon the action mechanism, are necessary.

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most serious adverse effects of chemotherapy. Platinum agents, including oxaliplatin, cisplatin (CDDP), and carboplatin (CBDCA), induce CIPN, and general symptoms of CIPN typically occur during the first 2 months of treatment, progress during active antineoplastic treatment, and then usually stabilize soon after treatment is completed [1, 2]. It persists for a certain period after the end of the causative drug and reduces patients' quality of life and activities of daily living. We experienced CBDCA-induced akathisia-like symptoms, which were significantly attenuated by pregabalin administration, and report its treatment.

Case Presentation

A man in his 40s who had been previously treated with 3 courses of CDDP (75 mg/m²) + pemetrexed (PEM, 500 mg/m²) and 32 courses of nivolumab (240 mg/body every 2 weeks or 480 mg/body every 4 weeks) for recurrent malignant pleural mesothelioma was administered CBDCA (area under the curve 5) + PEM (500 mg/m²) as the third-line treatment. He rarely experienced mild akathisia-like symptoms on his feet (nervous, uneasy, twitchy, restless, and instinct to move) before the diagnosis. The patient stated that he exhibited mild degradation of the symptoms that lasted during CDDP + PEM treatment, which did not require any pharmacotherapy. The patient rarely developed symptoms again during nivolumab treatment. However, the symptoms notably worsened to grade 2 approximately 7 days after the first cycle of CBDCA + PEM and did not disappear. Lorazepam (0.5 mg) was administered 3 times a day from day 14 but was not effective. He complained that the severity of the symptoms was much stronger than that in the CDDP + PEM treatment, and interestingly, symptoms became severe during the day and became milder (almost disappeared) at night. Therefore, we considered that the symptoms were different from restless legs syndrome and that it could be akathisia. However, the patient did not have brain metastasis, infection, or head injury. In addition, his regular medication included 40 mg of the probiotic *Clostridium butyricum* MIYAIRI, 200 mg of ursodeoxycholic acid, 2 mg of tizanidine, and 2.5 g of Shakuyaku-Kanzo-To, a herbal medicine, 3 times a day, and 10 mg of vonoprazan, 1 g of multivitamin, including 0.5 mg of folic acid, 100 mg of sustained-release ferrous fumarate, and 8 mg of sustained-release hydromorphone, once a day; all of them were previously administered before CBDCA + PEM treatment and did not induce the symptoms. In addition, palonosetron (0.75 mg) and dexamethasone (9.9 mg) infusion on day 1, dexamethasone (4 mg) orally on days 2 and 3, and oral aprepitant (125 mg) on day 1 and 80 mg on days 2 and 3 were administered for chemotherapy-induced nausea and vomiting prevention, which are also considered not to induce persistent symptoms. Consequently, the symptoms continued for 2 weeks from day 7 of the first chemotherapy, and we finally evaluated it to be derived from CBDCA-induced neuropathy as he experienced the same symptoms in CDDP + PEM treatment, although he did not exhibit typical CIPN indications, including numbness, tingling, and pain. Pregabalin is approved for peripheral neuropathy and is suggested to be effective for taxane-induced CIPN and antipsychotic-induced akathisia [3, 4]. Therefore, we decided to administer 75 mg pregabalin twice daily from the day of the initiation of the second course. As a result, the symptoms were significantly improved by its administration from the day of initiation, which he described as the symptoms having disappeared, even in the daytime, with grade 1 drowsiness. However, he complained that he felt the symptoms again after 10 h from the previous dose, which suggests that pregabalin was effective but its effect weakened or disappeared as time progressed. Chemotherapy was discontinued after the second course, and surgery was performed for disease control. The symptoms gradually improved after completion of chemotherapy.

Discussion

We encountered a patient who developed CBDCA-induced akathisia-like CIPN, which was significantly attenuated by pregabalin. We first suspected akathisia or restless legs syndrome. However, the patient did not take any suspected medicines and did not have any symptoms at night. Disease states that commonly cause akathisia include renal impairment, diabetes mellitus, hyperthyroidism, iron deficiency anemia, Parkinson's disease, and peripheral neuropathy [5, 6]. Moreover, Hening et al. [7] have reported that the diagnostic criteria for restless legs syndrome cannot rule out other possible confounding conditions, including nerve injury, including neuropathy. In addition, the ASCO guidelines suggest that neurological physical examination can be abnormal in CIPN diagnosis when the patient receiving neurotoxic chemotherapy develops new or worsening symptoms in their hands and/or feet, and there is no other good reason for the symptom development [1]. Therefore, it is difficult to distinguish them accurately during chemotherapy, and we considered it as CBDCA-induced CIPN.

Platinum agents are one of the most effective anticancer medicines for many types of malignancies but can induce CIPN [1, 2]. Although CBDCA uncommonly induces CIPN at standard doses [2], it is possible because the patient was previously administered CDDP and developed similar symptoms.

Pregabalin is thought to exert its analgesic action through antagonistic activity of voltage-gated Ca^{2+} channels, where it binds to the alpha-2-delta subunit [8, 9]. Gabapentin, which has a similar mechanism of action, has an effect on restless legs syndrome [10], and both of these medicines have been suggested to be effective for antipsychotic-induced akathisia [4, 11]. Salehifar et al. [3] also reported that pregabalin (150 mg daily) has superior CIPN attenuating effect compared to 60 mg of duloxetine, which is the only medicine recommended in the guidelines, and most patients in the study started the treatment during chemotherapy, as was the case for the patient in this report. Furthermore, 14.7% of Japanese patients discontinued duloxetine due to adverse effects [12]. Consequently, we considered that pregabalin was the most suitable medicine in this case, resulting in significant symptom attenuation.

Diabetes and increasing age have been shown to be strong independent risk factors for the development of CIPN [13]. In addition, concurrent exposure to other neurotoxic agents, pre-existing neuropathy, and smoking, as well as diseases/deficiencies per se predisposing to neuropathy, including alcohol abuse, renal insufficiency, hypothyroidism, vitamin deficiency, infections, including human immunodeficiency virus, and autoimmune rheumatologic conditions, should also be considered as potential risk factors [2]. The patient had previously experienced akathisia-like symptoms before chemotherapy; therefore, this background may have affected symptom development.

In conclusion, akathisia-like symptoms caused by CBDCA-induced CIPN are rare, but they significantly reduce quality of life. Pregabalin was significantly effective in this case; therefore, we suggest that a detailed symptom interview and selection of the medicine, considering the mechanism of action, are necessary for its management.

Statement of Ethics

We report this case in compliance with the Declaration of Helsinki. Informed written consent was obtained from the patient for the publication of the clinical data. Case reports are granted an exemption from requiring ethical approval at Hokkaido University Hospital.

Conflict of Interest Statement

All authors have no conflicts of interest.

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Author Contributions

Y.S. contributed to the design of the report, collected the data, and drafted the manuscript. Y.T., M.F., and M.S. revised the manuscript. All authors have read and approved the final manuscript.

Data Availability Statement

All data generated during this study are included in this article.

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