

Case Report

Combination of Mirogabalin and Duloxetine Attenuates Peripheral Neuropathy by Eribulin: A Novel Case Report

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Keywords

Chemotherapy-induced peripheral neuropathy · Mirogabalin · Duloxetine · Eribulin

Abstract

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most severe complications associated with chemotherapy for breast cancer. We encountered a case in which mirogabalin initially ameliorated, and additional duloxetine further attenuated eribulin-induced CIPN. Herein, we report its management. A 53-year-old woman received eribulin treatment as third-line chemotherapy for recurrent breast cancer. She experienced grade 2 CIPN with adjuvant docetaxel and cyclophosphamide treatment (worst numeric rating scale (NRS) 6/10 for numbness and 6/10 for pain) and had baseline grade 1 symptoms only in the hands (NRS 1/10 for each). CIPN in the hands and feet worsened to NRS 3/10 on day 1 of cycle 4. Mirogabalin (5 mg twice daily) was initiated, resulting in stable symptoms for approximately 6 weeks with grade 1 somnolence and heaviness of the head. The dosage was increased with careful attention to adverse effects to 22.5 mg per day, and the NRS was reduced from 5/10 to 3/10 for numbness and from 8/10 to 5/10 for pain. We administered duloxetine 20 mg with domperidone (10 mg three times a day) for further pain attenuation on day 1 of cycle 15, decreasing the NRS to 1/10 for numbness and 3/10 for pain. Duloxetine was increased due to CIPN degradation (NRS 3/10 and 5/10), resulting in a significant pain attenuation to 1/10. As the CIPN-attenuating mechanisms of mirogabalin and duloxetine are different, we consider that the additive and synergetic effects of this combination affected the results. Combination therapy with these drugs may be a promising strategy.

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Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most severe complications caused by drugs used in metastatic breast cancer treatment, such as taxanes, vinorelbine, and eribulin [1]. CIPN generally occurs during the first 2 months of treatment, progresses during antineoplastic treatment, and usually persists for a certain period after the end of the causative drug [2, 3]. It can significantly decrease patients' activities of daily living and quality of life. Duloxetine is a selective serotonin and noradrenaline reuptake inhibitor and is the only recommended drug in CIPN management guidelines [2, 3]. Mirogabalin is a selective $\alpha 2\delta$ ligand approved for treating peripheral neuropathic pain [4]. Eribulin mesylate is an inhibitor of microtubule dynamics. It produced a significant clinically meaningful improvement in overall survival compared to physicians' choice of treatment in patients with metastatic breast cancer receiving heavy chemotherapy [5]. In this study, 35% of the patients experienced CIPN, including approximately 8% with \geq grade 3 symptoms [5]. We encountered a case in which mirogabalin first ameliorated and additional duloxetine further attenuated eribulin-induced CIPN. Herein, we report its management.

Case Presentation

A 53-year-old woman with controlled acromegaly and postoperative pituitary adenoma was diagnosed with left breast cancer, which was excised (stage IIA, estrogen receptor expression [100%], progesterone receptor expression [100%], human epidermal growth factor type 2 negative, Ki-67 20.8%, WHO historical grade 3), followed by adjuvant docetaxel and cyclophosphamide (TC, 4 cycles), radiation (50 Gy/20 fractions), and administration of tamoxifen with luteinizing hormone-releasing hormone agonist. Approximately 5 years after the surgery, tumor recurrence with left axillary and infraclavicular lymph node metastases was confirmed. After the recurrence, she received chemotherapeutic treatment by letrozole (2.5 mg daily) with palbociclib (125 mg day 1–21, every 4 weeks) and EC (epirubicin 90 mg/m² + cyclophosphamide 600 mg/m², every 3 weeks). After eight cycles of EC treatment, disease progression was confirmed, and eribulin (1.4 mg/m² on days 1 and 8, every 3 weeks) was commenced. On days 8 and 15 of the first cycle, grade 4 neutropenia was confirmed, and the dose reduction to 1.1 mg/m² was initiated in the second cycle. However, grade 3/4 neutropenia developed in the third cycle, and the administration method was changed to 0.7 mg/m² biweekly from fourth cycle. She was a nonsmoker and social drinker with normal liver and renal function at baseline and received 10 mg of rabeprazole once a day and 330 mg of magnesium oxide three times a day during the treatment.

She had experienced grade 2 CIPN in her hands and feet in a previous TC (worst numeric rating scale (NRS) 6/10 for numbness and 6/10 for pain) and had baseline grade 1 symptoms only in the hands (NRS 1/10 for both). The process of her NRS score during the treatment is shown in Figure 1. She claimed that numbness in her hands slightly worsened on day 21 of the second eribulin cycle, and the symptoms gradually worsened in both hands and feet. We tried to initiate mirogabalin; however, she refused because of anxiety regarding its adverse effects. Finally, the symptoms reached NRS 3/10 for both, and she decided to receive mirogabalin 5 mg twice daily on day 1 of cycle 4, resulting in stable symptoms for approximately 6 weeks with grade 1 somnolence and heaviness of the head. Symptoms further deteriorated to NRS 5/10 for numbness and 8/10 for pain on day 1 of cycle 7. Therefore, mirogabalin was increased to 10 mg twice a day, but its dosage was reduced to 5 mg in the morning and 10 mg in the evening because of heaviness of the head, with symptom attenuation to NRS 4/10 and 7/10. On day 15 of cycle 10, the dosage was increased to 7.5 mg at morning and 15 mg at evening

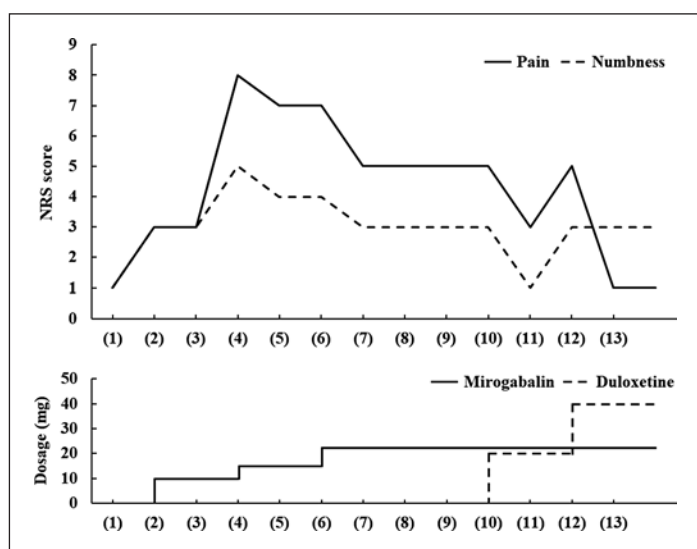


Fig. 1. Variations in NRS during eribulin treatment and dosage of mirogabalin and duloxetine. (1) Baseline characteristics before eribulin administration. (2) Mirogabalin 5 mg twice daily initiation: day 1 of cycle 4. (3) Stable symptoms: day 15 of cycle 6. (4) Symptom degradation, mirogabalin increased to 15 mg/day: day 1 of cycle 7. (5) Symptom attenuation: day 15 of cycle 7. (6) Mirogabalin increase to 22.5 mg daily: day 15 of cycle 10. (7) Symptom attenuation: day 1 of cycle 11. (8) Celecoxib 100 mg twice daily and VB12 0.5 mg three times daily initiation: day 1 of cycle 13. (9) Temporary pain attenuation: day 15 of cycle 13. (10) Duloxetine 20 mg once a day initiation: day 1 of cycle 15. (11) Continuous symptom attenuation: day 15 of cycle 15. (12) Symptom degradation: duloxetine increase to 40 mg once a day: day 15 of cycle 17. (13) Pain attenuation: day 1 of cycle 18.

with careful attention to adverse effects, resulting in a decrease to NRS 3/10 and 5/10. As she still claimed toilsomeness of CIPN pain with nausea for several days after eribulin administration, celecoxib 100 mg twice daily and VB12 0.5 mg three times a day were administered for pain alleviation on day 1 of cycle 13, resulting in pain NRS reduction to 3/10. However, symptoms' relief continued for only 2 h. Consequently, we decided to administer 20 mg of duloxetine with 10 mg of domperidone three times a day on day 1 of cycle 15, decreasing the NRS to 1/10 for numbness and 3/10 for pain, with grade 1 nausea and somnolence. After 10 weeks (day 15 of cycle 17), the symptoms worsened to 3/10 and 5/10 with nausea and somnolence attenuation (almost disappeared); therefore, the duloxetine dosage was increased to 40 mg per day. After duloxetine treatment, CIPN pain significantly decreased to 1/10, and numbness was stable. The mirogabalin dosage was deferred as CIPN worsened with dose reduction after increased duloxetine administration.

Discussion

CIPN management is one of the most important missions for the provision of less-onerous chemotherapy. In particular, because breast cancer chemotherapy is usually conducted in an outpatient setting, its incidence significantly reduces patients' quality of life and activities of daily living [2, 3, 6, 7]. However, evidence-based effective CIPN treatment is limited [2, 3].

Duloxetine is the only agent recommended in CIPN management guidelines [2, 3]. However, Salehifar et al. [8] reported that pregabalin has a higher CIPN attenuating efficacy than duloxetine, and most patients in that study started CIPN treatment during chemotherapy, which is

similar to our patient. Mirogabalin is reported to have a longer dissociation half-life for the $\alpha\delta$ -1 subunit, which is associated with analgesic effects, than pregabalin [9]. Furthermore, Sugimoto et al. [10] suggested that mirogabalin has a superior CIPN-attenuating effect to pregabalin, although both medicines are effective at improving CIPN in pancreatic cancer treatment. As previously mentioned, since the CIPN attenuating mechanisms of mirogabalin and duloxetine are different, we consider that the additive and synergetic effects of combination use affected the results. This is the first case report to suggest the CIPN attenuating efficacy of a combination of mirogabalin and duloxetine. As duloxetine efficacy was not confirmed in approximately 40% of patients [6], this result provides a further strategy for CIPN management.

In contrast, 14.7% of Japanese patients discontinued duloxetine because of adverse effects, such as fatigue and nausea [7]. Moreover, mirogabalin induces somnolence and dizziness, although most of the symptoms are mild or moderate [11]. As adverse effects related to central nervous system disorders are duplicated symptoms in combination, we should cautiously monitor these symptoms, especially during combination initiation and increase of dose. Furthermore, gastrointestinal management, such as nausea prevention by dopamine-2 receptor antagonists in duloxetine induction, is also necessary. In this case, we selected regular administration of domperidone, 10 mg three times a day, as the patient had already received this medicine for breakthrough nausea management without adverse effects, resulting in good nausea control without aggravation of eribulin-induced adverse effects. In addition, because mirogabalin is excreted from the kidney, its dosage should be adjusted according to the patient's renal function [11].

Taxanes, platinum, vincaalkaloids, eribulin, bortezomib, and thalidomide induce CIPN [2, 3]. In this patient, CIPN was induced by eribulin, which is classified as a halichondrin [5]. It has been reported that the clinical presentation of CIPN differs in each drug category owing to the nerve injury site [3]; therefore, it is necessary to confirm whether the combination is effective in other CIPN-provoking treatments, particularly with frequently used agents, such as taxanes and platinum. In addition, a randomized study implementation is strongly desired for appropriate evaluation.

In conclusion, combination therapy with mirogabalin and duloxetine was effective for eribulin-induced numbness and neuropathic pain. Cautious CIPN management enables continuous chemotherapy, and this combination could be a promising strategy.

Statement of Ethics

This case is reported in compliance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of the details of the medical case and any accompanying images. Case reports were granted exemption from requiring ethics approval at the Hokkaido University Hospital.

Conflict of Interest Statement

All authors have no conflicts of interest.

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Author Contributions

Yoshitaka Saito contributed to the design of the report, collected data, and drafted the manuscript. Yoh Takekuma, Tomohiro Oshino, and Mitsuru Sugawara revised the manuscript accordingly and approved the final version of the manuscript.

Data Availability Statement

All data generated during this study are included in this article. Further inquiries can be directed to the corresponding author.

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