Usefulness of Duloxetine for Paclitaxel-Induced Peripheral Neuropathy Treatment in Gynecological Cancer Patients

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Abstract. Aim: The present study aimed at evaluating the usefulness and adverse effects of duloxetine treatment for paclitaxel-induced peripheral neuropathy in gynecological cancer patients. Patients and Methods: Medical records of gynecological cancer patients treated with duloxetine were retrospectively studied to evaluate the drug’s efficacy for paclitaxel-induced peripheral neuropathy. Results: Results from 25 patients showed that an improved response was observed in 14 (56%). By univariate and multivariate analysis, the patient’s age, tumor origin, regimen of chemotherapy, accumulated doses of paclitaxel or carboplatin, previous medication, maintenance dosage and timing of treatment with duloxetine were found not to be associated with the effectiveness of duloxetine treatment. Adverse effects with duloxetine were mild and well-tolerated. Conclusion: As an option, duloxetine can be effectively used for paclitaxel-induced peripheral neuropathy in patients with gynecological cancers, irrespective of patients’ age, origin of the tumor, regimen of chemotherapy, or previous medication.

Taxanes (e.g., paclitaxel) and platinum compounds (e.g., carboplatin) are widely and effectively used in chemotherapy for gynecological cancers (1-4). However, as a trade-off, reportedly as often as 57% to 83% of the time, these agents cause painful chemotherapy-induced peripheral neuropathy (CIPN), a common toxicity associated with multiple chemotherapeutic agents. A typical dose of paclitaxel (175 mg/m²) is associated with severe CIPN in 2% to 12% of cases. CIPN is a grade 3 to grade 4 sensory neuropathy, based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (5). Calhoun et al. reported that ovarian cancer patients complaining of CIPN show a trend for worsening quality of life scores associated with increasing neurotoxicity (6). CIPN often results in delays, dose reduction, changing or even discontinuation of chemotherapy, thus the pain associated with cancer and cancer treatment is a serious health problem. Although the reasons for cancer and non-cancer neuropathic pain are different, the pathophysiological mechanisms are similar. There have been efforts to standardize pain treatment in order to provide better medical care.

Currently, the treatment options for CIPN are quite limited. To date, no drug has been approved specifically for treating CIPN pain. Opioids are a mainstay of cancer pain treatment, but are not suitable for chronic pain because of their addictive effects. However, a new group of chronic pain therapeutics called co-analgesic drugs has been introduced. These include topical agents, anti-depressants and anti-convulsants, e.g., gabapentinoids (gabapentin, pregabalin), anti-depressants (tricyclic antidepressants, duloxetine, and venlafaxine), corticosteroids, bisphosphonates, N-methyl-D-aspartate antagonists, and cannabinoids (7) Duloxetine, a balanced serotonin-norepinephrine reuptake inhibitor (SNRI), has the most evidence supporting its use in the treatment of CIPN (8).

A topical pain cream can contain baclofen, amitriptyline and ketamine. Barton et al. reported that such topical agents had little efficacy for CIPN (9). Two studies have evaluated the efficacy of tricyclic anti-depressants for CIPN. Neither study showed a sufficient effect of the anti-depressants for CIPN, and given their significant adverse effects, doctors do not consider tricyclics to be first-line agents for CIPN (10; 11). Similarly, anti-cholinergic, anti-histaminergic and anti-
adrenergic pain drugs produce adverse effects such as dry mouth, drowsiness, weight gain and hypotension. Although anticonvulsants are often used for many other types of neuropathic pain, the clinical evidence does not support their efficacy for CIPN (12).

Duloxetine inhibits serotonin and norepinephrine synaptic reuptake, causing their synaptic concentrations to increase, thus blocking input signals to the spinal dorsal horn neurons, which results in decreased pain transmission (13). At present, duloxetine, under the trade name Cymbalta, is approved by the Food and Drug Administration (FDA) to treat major depressive disorder and general anxiety disorder, fibromyalgia (a chronic pain disorder), and chronic muscle or joint pain (such as low back pain and osteoarthritis pain). Duloxetine is licensed and very widely used to treat pain caused by nerve damage in people with diabetes (diabetic neuropathy) (13).

Thus, duloxetine could reasonably be expected to be an effective agent for CIPN. We conducted this study to explore duloxetine’s potential for clinical effectiveness against CIPN specifically in gynecological cancer patients receiving paclitaxel chemotherapy.

Materials and Methods

Medical records of gynecological cancer patients treated with duloxetine for paclitaxel-induced peripheral neuropathy at the Osaka University Hospital from March 2012 to July 2013 were evaluated retrospectively regarding the drug’s efficacy and adverse effects. The severity of neuropathic pain or numbness was evaluated according to the NCI-CTCAE (v. 4.0).

From the patient’s medical records, we utilized the grade of CIPN provided by the attending doctors or nurses. By comparing the patient’s condition before and after duloxetine administration, we evaluated the patient response either as ‘responders’; those cases for which the neuropathy dropped more than 1 grade, or as ‘non-responders’; cases which had a stable or worsening grade of neuropathy following treatment. Cases whose efficacy we could not fairly evaluate were excluded from the analysis.

Statistical analysis. Categorical data were analyzed by the Fisher’s exact test. A Cox proportional hazards regression model was used for multivariate analysis to find independent factors affecting the efficacy of duloxetine. Statistical results were considered to be significant when the p-value was less than 0.05.

Results

Clinical characteristics of patients. Patients’ characteristics are shown in Table 1. The median age was 62 years (range=40-77). Tumor origins were as follows: 16 ovarian, 7 corpus, and 2 cervical cancers. With respect to chemotherapy regimens, 20 patients received TC (paclitaxel +carboplatin), and five patients underwent TEC (paclitaxel+epirubicin+ carboplatin). The median accumulated dose of paclitaxel was 1,805 (range=634-4,697) mg/body. The median accumulated dose of carboplatin was 3,368 (range=1,350-7,898) mg/body.

Table 1. Patients’ characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>median: 62 (40-77)</td>
</tr>
<tr>
<td>Tumor origin</td>
<td></td>
</tr>
<tr>
<td>Ovary</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>Endometrium</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>Cervix</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td></td>
</tr>
<tr>
<td>TC</td>
<td>20 (80%)</td>
</tr>
<tr>
<td>TEC</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Accumulated dose of PTX</td>
<td>median: 1805 (634-4697) mg/body</td>
</tr>
<tr>
<td>Accumulated dose of CBDCA</td>
<td>median: 3368 (1350-7898) mg/body</td>
</tr>
<tr>
<td>Previous medication for CIPN</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Goshajinkigan</td>
<td>10 (40%)</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>VitB12 agent</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>SSRI</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>

TC, Paclitaxel/carboplatin; TEC, paclitaxel/epirubicin/carboplatin; PTX, paclitaxel; CBDCA, carboplatin; CIPN, chemotherapy induced peripheral neuropathy; VitB12 agent, vitamin B12; SSRI, selective serotonin reuptake inhibitors.

In 10 cases (40%), duloxetine was the first medication administered for CIPN. In 15 cases (60%), other drugs for neuropathy were administered prior to duloxetine. Other medications included goshajinkigan, pregabalin, Vitamine-B12 agent (VitB12) and SSRI. A maintenance dosage of duloxetine of 20 mg/day was given in 18 cases (72%), the other seven cases (28%) received 40 mg/day. Duloxetine was started during chemotherapy in 12 cases (48%), and after completing chemotherapy in 13 cases (52%), including nine cases in which duloxetine was started within 1 year from chemotherapy, and four cases where duloxetine was started 1 year after chemotherapy.

Association between the patients’ clinical characteristics and efficacy of duloxetine. We divided the cases into responders and non-responders and investigated for any association between several different clinical characteristics and the patient’s responsiveness to duloxetine. These characteristics included age (≤60 or >60), origin of the tumor (ovary or uterine endometrium/cervix), regimen of chemotherapy (TC or TEC), accumulated dose of paclitaxel (≤1,800 or >1,800 mg/body), previous treatment with neuropathy medication (+ or –), level of maintenance dosage of duloxetine (20 or 40 mg/day) and timing of treatment (during chemotherapy or after chemotherapy). Using the Fisher’s exact test, we observed no significant association between any of these patient factors and the perceived effectiveness of duloxetine
treatment (Table II). Moreover, a multivariate analysis using the Cox proportional hazards regression model found no independent factors affecting the efficacy of duloxetine (Table II). We did note that duloxetine tended to have somewhat lesser efficacy in patients older than 60 years.

Adverse events. Adverse events among the 25 cases were very mild and usually well-tolerated. Somnolence (n=3, 12%), giddiness (n=3, 12%), nausea (n=1, 4%), constipation (n=1, 4%) and dysgeusia (n=1, 4%) were observed (Table III). Two patients (8%) discontinued duloxetine because of its adverse effects, which for them included somnolence and giddiness.

Discussion

Pain treatment is a challenge, given the diverse mechanisms of pain and variable responses in individuals. However, most patients derive pain relief from a well-chosen monotherapy or well-designed polypharmacy that combines agents with different mechanisms of action (14).

There have been several previous reports concerning the efficacy of monotherapy with duloxetine for the treatment of CIPN for other types of tumors, as reviewed by Hershman et al. (8). Yang et al. conducted an open-label pilot study of duloxetine in 39 patients with colorectal cancer treated by oxaliplatin chemotherapy (15). They found duloxetine to be useful for treating their oxaliplatin-induced neuropathy; 23% of their cases (9/39) showed improvement of one or more grade. However, in their study (which used a higher maintenance dose of 60 mg/day, instead of the 20 or 40 mg/day used in our study) they also had nine patients (23.1%) who discontinued duloxetine before the end of treatment because of adverse events. On the positive side, they found that treatment with duloxetine did not impair renal or liver function and did not interfere with chemotherapy.

In a randomized phase III double-blind crossover trial of duloxetine versus placebo for painful CIPN, the use of duloxetine after paclitaxel, other taxanes, or oxaliplatin treatment resulted in a greater reduction in pain compared to...
a placebo (16). In yet another study, Takenaka et al. reported that severe paclitaxel-induced peripheral neuropathy, which wasn’t responsive to pregabalin/trazodone, remitted following treatment with pregabalin/duloxetine (17).

In our present study, we have retrospectively evaluated the efficacy and usefulness of duloxetine in our gynecological cancer patients treated with a standard chemotherapy using paclitaxel and carboplatin with or without epirubicin. Response (improvement) was observed in 56% of our cases (14/25). The accumulated doses of paclitaxel and carboplatin did not correspond to whether the patient was a responder or non-responder. Similarly, age (<60 or >60), origin of the tumor (ovary or endometrium/cervix), regimen of chemotherapy (TC or TEC), previous neuropathy medication (+ or –), maintenance dosage of duloxetine (20 mg/day or 40 mg/day) and timing of treatment (during chemotherapy or after chemotherapy) were not associated with the effectiveness of duloxetine treatment, by a univariate and a multivariate analysis.

These results suggest that there are as yet no significant predictive or precautionary factors for the effectiveness of duloxetine, and that duloxetine can be effectively used in gynecological cancer patients irrespective of the patients’ age, origin of the tumor, regimen of chemotherapy, previous medication, and maintenance dosage of duloxetine and timing of treatment.

This does not suggest that the drug is completely safe. According to the manufacturer, duloxetine, sold under the trade name Cymbalta, has dangerous interactions with a number of other drugs, including MAO inhibitors, furazolidone, isocarboxazid, linezolid, phenelzine, rasagiline, selegiline, and tranylcypromine. Known side-effects include mood or behavior changes, anxiety, panic attacks, trouble sleeping, impulsive, irritable, agitated, hostile, aggressive, or restless feelings, hyperactivity (mentally or physically), increased depression, and thoughts about suicide or hurting oneself. The frequency of potential drug-drug interactions (DDIs) and drug-condition interactions (DCIs) were studied in 1,354 patients with painful diabetic peripheral neuropathy (DPN) treated with duloxetine. Among duloxetine users, 966 (71%) had at least one potential duloxetine DDI or DC I (18).

We observed that elderly cases (>60 years) tended to be somewhat less responsive of duloxetine. Adverse events were observed in 50% (7/14) of elderly cases versus only 18% (2/11) in younger patients. Although the difference was not statistically significant (p=0.21), elderly patients tended to complain more about taking the drug than younger patients (data not shown). Four out of seven elderly patients complaining of adverse effects were assessed as non-responders and duloxetine was discontinued without first attempting to increase the dosage. Moreover, two of the elderly ‘responders’ desired to discontinue duloxetine because of their adverse effects.

An even higher dosage of duloxetine might be useful for those cases in our study that did not suffer adverse effects at the dosage used; however, the higher maintenance dosage of duloxetine (20 mg/day versus 40 mg/day) was not associated with improved effectiveness. Duloxetine is approved as a first-line agent for diabetic peripheral neuropathy with pregabalin. The maintenance dosage recommended is a dose of 60 mg /day (19). In some previous studies, patients were administered a dosage of 60 mg/day duloxetine for their CIPN (15, 16). In our study, the majority of patients (18/25) received only the minimum dosage of 20 mg/day.

Six out of the 11 non-responders in our study had no adverse effects with their dosages (20 mg/day: n=4; 40 mg/day: n=2). It is possible that an increased dosage of duloxetine would have been beneficial, if it had been attempted. Future studies might try titrating upward to where adverse effects are noted in the individual patient, then backing away to a tolerable dose.

The present study was retrospective. There is no universally-accepted, well-validated measure for the assessment of CIPN. There was no choice but to evaluate the efficacy of duloxetine for CIPN only by NCI-CTCAE v4. NCI-CTCAE is a widely used physician-based scale to evaluate mainly restrictions of daily life quality, but it is ambiguous for neuropathy symptoms and is not able to evaluate for slight improvements. To date, a gold standard scale for evaluating CIPN has not been defined. Patient-based assessments include the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (Fact/GOG-Ntx) scale and the Patient Neurotoxicity Questionnaire (PNQ). It is preferred to include in the evaluation of drug efficacy for CIPN both a physician-based and patient-based assessment of response. Routine assessment should continue for a prolonged period because CIPN is known to progress with chemotherapy-dose accumulation and lingers long after chemotherapy cessation (5).

In conclusion, we showed that duloxetine is a useful treatment option for the treatment of paclitaxel CIPN in patients with gynecological malignancies.

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References


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