Pilot Study of Duloxetine for Cancer Patients with Neuropathic Pain Non-responsive to Pregabalin

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Abstract. Background: Neuropathic pain frequently occurs in cancer patients, but no drug therapy has been established for this type of disorder. The purpose of this study was to investigate the effect of duloxetine in cancer patients suffering from neuropathic pain. Patients and Methods: The subjects of the study were 15 cancer patients with neuropathic pain who visited the Kinki University Faculty of Medicine Hospital and met the International Association for the Study of Pain diagnostic criteria for neuropathic pain. Duloxetine was administered to patients in whom pregabalin could not be administered. The influence of duloxetine was investigated retrospectively with the use of a numerical rating scale. Results: Pain was reduced in 7 out of the 15 patients. Sleepiness and the light-headed feeling were improved in four patients, in whom, however, the pain was not reduced. Thus, duloxetine was judged to be effective in 11 patients. The maintenance dose of duloxetine was 20-40 mg/day. Conclusion: Duloxetine administration may be effective for neuropathic pain in cancer patients who cannot tolerate pregabalin administration.

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Key Words: Colorectal, breast, lung, cancer, neuropathic pain, duloxetine, pregabalin, adverse effects.
The efficacy of duloxetine for diabetic NP and fibromyalgia has been widely investigated, but few studies have been performed for cancer patients, with only one report on the effect of duloxetine on chemotherapy-induced peripheral neuropathy (18). Therefore, the objective of this study was to investigate the effect of duloxetine in cancer patients with NP in whom pregabalin treatment was unsuccessful.

Patients and Methods

This study was performed at the Kinki University Faculty of Medicine Hospital, in Osaka, Japan. We retrospectively analyzed 15 cancer patients (9 males and 6 females). The subjects of this study were cancer patients who visited the Kinki University Faculty of Medicine Hospital between April 2011 and October 2011 and met the International Association for the Study of Pain (IASP) diagnostic criteria for NP (19).

None of the patients had major frequent causes of NP not related to cancer, such as diabetes or microangiopathy. Two psychoncologists performed diagnosis for mental disorders, and no patients met the criteria (20) for depression and anxiety disorder.

Opioids were administered to the patients who suffered from excruciatingly severe pain the opioid treatment, but some patients did not receive opioids because they only suffered from chemotherapy-induced peripheral neuropathy and did not wish to take them. The first 15 cancer patients were diagnosed with NP by the IASP diagnostic criteria for NP. The patients were treated with duloxetine because pregabalin could not be administered, was ineffective, or was effective but the dose could not be elevated due to adverse effects. Pregabalin had been discontinued in these patients: nine patients had sleepiness, seven had an unpleasant light-headed feeling and one patient had edema. Two out of the 15 patients had two adverse effects of pregabalin.

An analgesic effect of duloxetine has been reported at one week after initiation of administration for diabetic NP (21). However, we thought that a longitudinal assessment over a far longer period

Table I. Clinical characteristics of the patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>PS</th>
<th>Cancer type</th>
<th>Cause of pain</th>
<th>Analgesic Opioid Pregabalin</th>
<th>Adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71</td>
<td>M</td>
<td>1</td>
<td>Unknown</td>
<td>PTX</td>
<td>No</td>
<td>150 Sleepiness</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>M</td>
<td>2</td>
<td>CRC</td>
<td>FOLFOX</td>
<td>Yes Sustained release</td>
<td>300 Sleepiness</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>M</td>
<td>2</td>
<td>CRC</td>
<td>XELOX</td>
<td>Yes Sustained release</td>
<td>300 Sleepiness</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>M</td>
<td>1</td>
<td>CRC</td>
<td>FOLFOX</td>
<td>Yes Sustained release</td>
<td>No Sleepiness</td>
</tr>
<tr>
<td>5</td>
<td>76</td>
<td>M</td>
<td>1</td>
<td>Lung</td>
<td>PTX</td>
<td>Yes No</td>
<td>No Sleepiness, light-headed feeling</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>F</td>
<td>2</td>
<td>Breast</td>
<td>Spinal cord invasion</td>
<td>Yes Sustained release morphine, 30 mg</td>
<td>No Light-headed feeling</td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>M</td>
<td>2</td>
<td>CRC</td>
<td>XELOX</td>
<td>No No</td>
<td>150 Sleepiness</td>
</tr>
<tr>
<td>8</td>
<td>72</td>
<td>M</td>
<td>3</td>
<td>Lung</td>
<td>Spinal cord invasion</td>
<td>Yes Sustained release oxycodone, 640 mg</td>
<td>No Sleepiness</td>
</tr>
<tr>
<td>9</td>
<td>79</td>
<td>M</td>
<td>3</td>
<td>Lung</td>
<td>Spinal cord invasion</td>
<td>Yes Sustained release oxycodone, 30 mg</td>
<td>225 Light-headed feeling</td>
</tr>
<tr>
<td>10</td>
<td>44</td>
<td>F</td>
<td>1</td>
<td>Breast</td>
<td>PTX</td>
<td>No No</td>
<td>125 Sleepiness, edema</td>
</tr>
<tr>
<td>11</td>
<td>61</td>
<td>F</td>
<td>1</td>
<td>Breast</td>
<td>PMPS</td>
<td>No No</td>
<td>150 Light-headed feeling</td>
</tr>
<tr>
<td>12</td>
<td>75</td>
<td>1</td>
<td>CRC</td>
<td>Spinal cord invasion</td>
<td>Yes Transdermal fentanyl, 1 mg</td>
<td>No Light-headed feeling</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>40</td>
<td>F</td>
<td>1</td>
<td>Breast</td>
<td>PTX</td>
<td>No No</td>
<td>150 Sleepiness</td>
</tr>
<tr>
<td>14</td>
<td>59</td>
<td>M</td>
<td>1</td>
<td>CRC</td>
<td>Spinal cord invasion</td>
<td>Yes No</td>
<td>No Sleepiness</td>
</tr>
<tr>
<td>15</td>
<td>68</td>
<td>F</td>
<td>1</td>
<td>Breast</td>
<td>NabPTX</td>
<td>No No</td>
<td>150 Light-headed feeling</td>
</tr>
</tbody>
</table>

CRC, Colorectal cancer; PS, performance status; FOLFOX, leucovorin + 5-fluorouracil + oxaliplatin; XELOX, capecitabine + oxaliplatin; PTX, paclitaxel; NabPTX, abraxane; PMPS, postmastectomy pain syndrome; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs.
should be performed. Therefore, we evaluated the scale at one week after administration and two to four weeks after administration. Duloxetine was classified as ‘effective’ in patients in whom it was administered for ≥4 weeks, and ‘ineffective’ in those at whom the drug was discontinued within four weeks. Concomitant treatment with analgesics, such as opioids and other adjuvant analgesics was not changed throughout the study period.

Results

Clinical characteristics of the 15 patients are presented in Table I, including Eastern Cooperative Oncology Group Performance Status (PS) on the first day of duloxetine administration and of the use of concomitant opioids and NSAIDs. Pain was reduced in 7 out of the 15 patients and sleepiness and a light-headed feeling were improved in four patients in whom pain was not reduced. Thus, duloxetine was judged to be ‘effective’ in 11 patients (Table II). In the remaining four patients, no effect on pain was observed in three cases, and duloxetine was discontinued at 2 weeks because there was also no improvement of adverse effects. In the other case, continuation of duloxetine was difficult due to decrease in PS. The maintenance dose of duloxetine was 20-40 mg/day in patients who received duloxetine for ≥2 weeks.

Discussion

The pain was reduced in 7 out of the 15 patients and the adverse effects were improved in four patients, indicating that duloxetine was effective in 11 patients. NP caused by peripheral neuropathy as an adverse effect of anticancer drugs requires treatment since it impairs the quality of life (QOL) of patients and may lead to suspension or discontinuation of the anticancer treatment. However, NP may often be overlooked, since attending physicians has been found to diagnose diabetic neuropathy (benign disease-associated NP) in only half of the patients (22). Moreover, pain in cancer patients is likely to be underestimated, with a lower estimation of pain reported in about 50% of patients (23). In addition, in a study performed on lung cancer patients, fewer than 30% of them were able to explain their concerns to their physician (24). The pathological condition may be aggravated when anticancer treatment is continued in cases in which physicians underestimate NP caused as adverse effects of anticancer drugs and patients cannot convince the physician of the severity of the pain.

It has also been reported that 40% of cancer patients are in a depressive state that requires treatment (25) and that this depression may influence the rejection of the anticancer therapy (26). Therefore, treatment of depression is necessary, but this condition is difficult to be evaluated and is frequently overlooked by both physicians and nurses (27, 28). One reason is the marked overlap of cancer symptoms with the diagnostic criteria for depression, with physicians, nurses, and patients considering that ‘distress is natural because of cancer’. Psychomotor inhibition is a characteristic of depression, in which patients cannot organize their thinking and feel too distressed to talk (29). This may lead to a delay in treatment of NP and more attention should be attributed to this issue.

Pregabalin is frequently used as a first choice drug for NP, but causes diverse adverse effects including somnolence, a light-headed feeling and edema (30). In addition, insomnia,
nausea, headache, and diarrhea have been reported as withdrawal symptoms (31). Suicidal ideation may also be induced by novel antiepileptics, with the risk of self-injurious behavior found to be increased three-fold by depressive state-inducing antiepileptics, although pregabalin has not been found to increase this risk (32). In contrast, the Health News Letter of Canada reported 16 cases of suicidal ideation and one suicide attempt in patients receiving pregabalin (33). Thus, careful administration of pregabalin is necessary, although the drug is effective for pain. Selection of an adjuvant analgesic requires consideration of adverse effects, in addition to the effect on pain, and an appropriate drug should be used for individual patients.

In a meta-analysis, Quilici et al. found that the efficacy of once-a-day duloxetine administration for diabetic NP was equivalent to those of pregabalin and gabapentin (34). In a RCT, Tanenberg et al. showed the non inferiority of 60 mg/day duloxetine compared to 300 mg/day pregabalin for diabetic NP in patients for whom gabapentin was ineffective (35). The study reported high incidences of nausea, anorexia, and insomnia in the duloxetine group and of edema in the pregabalin group. In 39 colorectal cancer patients with NP following oxaliplatin treatment, Yang et al. found that 30-60 mg/day duloxetine improved the score on a visual analog scale in 19 out of 30 patients in whom duloxetine could be continued (18). In our study, duloxetine was administered at a lower dose of 20-40 mg/day, which facilitated the continuation of administration while preventing pain aggravation. Mittal et al. showed that duloxetine has been suggested to have less effect on NP compared to pregabalin (36), while having a higher withdrawal rate due to adverse effects; however, this study was performed in non-cancer patients with diabetic NP. Duloxetine is reported to frequently cause nausea, but the incidence of adverse effects that are frequently induced by pregabalin, including edema, sleepiness, and a light-headed feeling, was low. Furthermore, duloxetine only requires administration once a day. These properties suggest that duloxetine may be a useful alternative treatment for patients to whom pregabalin cannot be readily administered.

There are several limitations of this study. Firstly, duloxetine may not have acted only on NP. About 40% of cancer patients have depression that requires treatment; the pain threshold decreases and the sensitivity to pain increases in patients in a depressive state (37). Since there are many uneasy and depressive patients among cancer patients, even if they do not meet the DSM-IV-TR criteria for diagnosis of depression and anxiety disorder, duloxetine may well be effective psychologically. In our study, no patients met the DSM-IV-TR criteria for diagnosis of depression, but it cannot be ruled out that the pain could have been reduced through elevation of the pain threshold due to an improvement in depression. There is a possibility that duloxetine was effective in both activation of the descending pain modulatory system and the improvement of depressive mood which does not meet the DSM-IV-TR criteria for diagnosis. Secondly, patients who could be readily investigated retrospectively were selected as subjects and the study was performed at a single hospital. This makes it difficult to generalize the results to other facilities. Moreover, the duration of illness, existant concomitant diseases, concomitant use of NSAIDs, drugs other than adjuvant analgesics, and the psychosocial background, such as the educational level and the employment, were not surveyed. Further studies are necessary in order to establish the effects of these factors.

Within these limitations, the results of this study suggest that duloxetine could reduce the NP and the adverse effects in cancer patients. This is also the first study to report the use of duloxetine for cases in which pregabalin could not be used. The effect may have partly taken place due to elevation of the pain threshold through the antidepressant effect of duloxetine. However, this may still be useful since many antidepressants cannot be readily administered to cancer patients and the depressive state of cancer patients is currently underestimated and often untreated (26, 27, 38).

Our results show that duloxetine may be useful for NP in cancer patients who cannot tolerate administration of pregabalin.

Conflicts of Interest

Authors report no declarations of interest.

References


