

Randomized Trial

Combinations of Low-Dose Antidepressants and Low-Dose Pregabalin as Useful Adjuvants to Opioids for Intractable, Painful Bone Metastases

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Background: Systemic analgesics would not provide good enough pain relief for some kinds of cancer pain. Metastatic bone pain is characteristic of one of the refractory cancer pains, since the pain is not only nociceptive but also neuropathic. A low-dose antiepileptic-antidepressant combination with opioids is effective in the management of neuropathic cancer pain.

Objective: The aim was to see whether a low-dose antiepileptic-antidepressant combination is effective in the treatment of bone metastases.

Study Design: Randomized, controlled trial

Setting: Pain Clinic in Japan.

Methods: Thirty-seven cancer patients, confirmed to have bone metastases, were allocated into 3 groups: P group took pregabalin 50 mg every 8 hours orally; P-I group took pregabalin 25 mg every 8 hours orally and imipramine 5 mg every 12 hours orally; P-M group took pregabalin 25 mg every 8 hours orally and mirtazapine 7.5 mg every 12 hours orally. Pain assessments were performed for 2 weeks.

Results: The total pain score significantly decreased in all 3 groups even one day after the start of the medication. The decreases in the P-I and P-M groups were significantly greater than those in the P group from Day 2. Also, the daily paroxysmal pain episodes significantly decreased in all 3 groups at Day 1. The decreases in the P-M groups were significantly greater than those in the P group from Day 1. The decreases in the P-I group were significantly greater than those in the P group from Day 3.

Conclusion: Low-dose pregabalin-antidepressant combinations with opioids were effective in the management of painful bone metastases.

Key words: Cancer pain, painful bone metastases, antidepressant and anticonvulsants, pregabalin, mirtazapin

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In the treatment of cancer pain, adequate pain relief has been obtained in a lot of cases by the recommended approach using systemic medications according to the World Health Organization analgesic ladder (1). However, systemic analgesics would not provide good enough pain relief for some kind of

cancer pains. Metastatic bone pain is characteristic of cancer pain and one of the refractory cancer pains (2,3). Although the complete mechanism is not yet fully characterized, metastatic bone pain exhibits components of both inflammatory and neuropathic pain (4-6). Standard treatment includes radiotherapy

and a pharmacologic approach using nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and bisphosphonates. However, the current standard treatment is inadequate for a sizeable number of patients (7).

Neuropathic pain results from a dysfunction of peripheral and central nerves (8,9). Neuropathic cancer pain often shows little response to non-opioid and opioid analgesics, but may be relieved by adjuvants such as antidepressants and antiepileptics (10,11). Also, we previously reported that a low-dose gabapentin-imipramine combination with opioids was effective in the management of neuropathic cancer pain (12). Since mirtazapine is one of the noradrenergic and specific serotonergic antidepressants, it is believed to have potential as an adjuvant analgesic (13,14). However, mirtazapine alone does not provide an improvement in cancer pain. For this reason, we hypothesized that mirtazapine would lead to an improvement in pain when combined with antiepileptics. We thus performed an evaluation of the analgesic effect of a low-dose antiepileptic-antidepressant combination on metastatic bone pain.

METHODS

Patients with intractable pain due to bone metastases were enrolled in this study from January 2010 to September 2011. Cancer metastases in bones were confirmed by bone scintigraphy and computed tomography (CT) in all patients. Approval from the local ethics committee and oral informed consent from the patients was obtained, and if the pain was not adequately relieved by opioids and NSAIDs, or the opioid dose was restricted by side effects, pregabalin and imipramine or mirtazapine were started after the first referral visit to our clinic.

In this randomized, controlled trial, the cancer patients were randomized to one of 3 groups using computer-generated random numbers:

1. P group: pregabalin 50 mg every 8 hours orally.
2. P-I group: pregabalin 25 mg every 8 hours orally and imipramine 5 mg every 12 hours orally.
3. P-M group: pregabalin 25 mg every 8 hours orally and mirtazapine 7.5 mg every 12 hours orally.

Previous 24-hour average intensity of total pain was assessed on 0 – 10 numerical scales and previous 24-hour paroxysmal pain (shooting or lancinating pain) episodes were recorded (12,15). Pain assessments were

performed at the first visit (Day 0) and one to 7 days and 10 and 14 days after the start of the medication. Opioid “rescue” doses were available as needed. NSAIDs that were already administered were kept unchanged. No new drug was started during this period. An electrocardiogram (ECG) was performed before and at the end of the study and estimated glomerular filtration rate (eGFR) was measured before the study in all patients.

Our previous study showed the mean (SD) of the total pain score at 7 days after the start of the combination medication to be 2.3 (1.5). Thus, the sample size of 12 was needed to show intergroup differences of 2.0 (1.5) with a significant level of 0.05 ($\alpha = 0.05$) and a power of 80% ($\beta = 0.20$). Data are presented as the median (range), number or the median with the twenty-fifth and seventy-fifth percentiles. Since the Kolmogorov-Smirnov test failed, the patients’ characteristics, daily opioid dose (oral morphine equivalent (16), pain score, and paroxysmal pain episodes were analyzed using the Kruskal-Wallis test for intergroup comparison or the Friedman test for intragroup comparison followed by Dunn’s method for multiple comparisons. Gender was analyzed by the chi-squared test. A P-value less than 0.05 was regarded as significant.

RESULTS

There were no significant differences in patient characteristics and daily opioid dose (oral morphine equivalents) among the 3 groups (Table 1). Loxoprofen sodium (180mg/day) and bisphosphonates were used in all patients. Acetaminophen up to 2400 mg was used in 2 patients in the P group, 3 in the P-I, and 3 in the P-M. There were no patients with advanced chronic kidney disease who required a dose reduction of drugs.

The 3 groups were comparable with respect to the total pain score and daily paroxysmal pain episodes at base (Figs. 1 and 2). The total pain score significantly decreased in all 3 groups even one day after the start of the medication (Fig. 1). The decreases in the P-I and P-M groups were significantly greater than those in the P group from Day 2. Also, the daily paroxysmal pain episodes significantly decreased in all 3 groups even one day after the start of the medication (Fig. 2). The decreases in the P-M groups were significantly greater than those in the P group from Day one. The decreases in the P-I group were significantly greater than those in the P group from Day 3. Since pain control was not sufficient in the P group, mirtazapine was prescribed at Day 7 and the patients were withdrawn from the present study. Then, the P-I and P-M groups were followed.

Table 1. Demographics and baseline characteristics of patients. Values are median (range) or number.

	P (n = 12)	P-I (n = 12)	P-M (n = 13)	P
Age (year)	64 (47-71)	54 (40-77)	64 (37-72)	0.4709
Sex (M/F)	8/4	8/4	8/5	0.9538
Weight (kg)	54 (40-64)	53.5 (36-70)	50 (43-68)	0.7877
Daily opioid dose ^a (mg/day)	60 (20-180)	55 (20-200)	60 (20-120)	0.9342
Oxycodone SR	6	7	7	
Fentanyl Patch	6	5	6	

^aOral morphine equivalent.

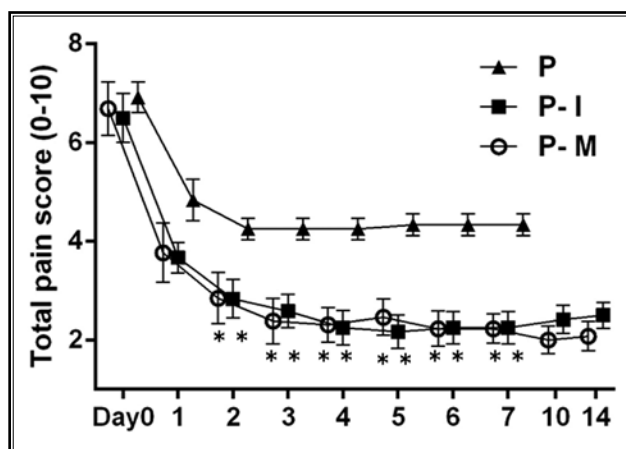


Fig. 1. Changes of the total pain score. P, pregabalin. P-I, pregabalin- imipramine. P-M, pregabalin- mirtazapine. Error bar represents standard error of the mean (SEM). * $P < 0.05$ vs pregabalin.

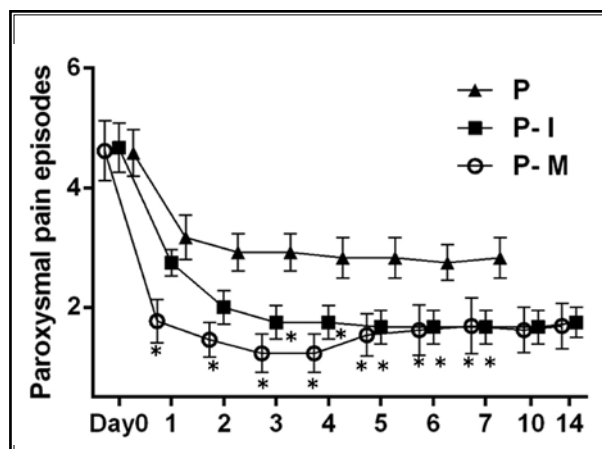


Fig. 2. Changes of the daily paroxysmal pain episodes. P, pregabalin. P-I, pregabalin- imipramine. P-M, pregabalin- mirtazapine. Error bar represents standard error of the mean (SEM). * $P < 0.05$ vs pregabalin.

The pain relieving effects in the P-I and P-M groups were maintained for one more week (Figs. 1 and 2). A few patients developed adverse symptoms such as mild dizziness and mild drowsiness in the 3 groups. Significant ECG abnormalities including QT interval prolongation did not develop during the study in any of the patients.

Discussion

Some cancer pain syndromes are intractable even with the use of opioid analgesics. There are multiple mechanisms in the pathophysiology. Metastatic bone pain includes neuropathic as well as nociceptive factors (4-6). A neuropathic pathophysiology leads to a refractory outcome to opioid use. This fact indicates the need for the use of non-opioid analgesics in combination with opioids. Antiepileptics and antidepressants are the most commonly used adjuvant analgesics in pain syndromes of cancer patients when a neuropathic factor is implied

from clinical observations (10,11). Thus, we intended to prescribe pregabalin, imipramine, and mirtazapine instead of increasing the opioid dose at the first visit in the present study.

Presently, antiepileptics, such as gabapentin and pregabalin, are widely used to relieve pain. They bind to the $\alpha 2\delta$ calcium channel subunits which are expressed in the central terminals of peripheral sensory nerves in the dorsal horn and inhibit the influx of calcium (17). Consequently, they inhibit signal transduction of pain by reducing the release of neurotransmitters (18). Several studies have confirmed that they are effective in the treatment of neuropathic pain caused by not only non-malignant but also malignant aetiology (19-25). Also, antiepileptics in combination with morphine or antidepressants provide better analgesia at lower doses of each drug than each drug alone (12,15,26-30). Morphine acts on opioid receptors located on neuronal

cell membranes and inhibits neurotransmitter release, which is considered to be the major mechanism of action responsible for its analgesic effects (31). The main proposed mechanism of action of antidepressants is reuptake inhibition of both serotonin and norepinephrine in the central nervous system, which increases the activity of these neurotransmitters and subsequently reduces the perception of pain by modulating the pain signals (19). Although these drugs are used in treating neuropathic pain (19), as monotherapy they are associated with limited efficacy and dose-related side effects. The combination of mechanically distinct analgesic agents is expected to result in additivity or synergism at lower doses and with fewer side effects than with the use of one drug alone.

Mirtazapine, which is a potent antagonist at central presynaptic α 2-autoreceptors, postsynaptic 5HT2 and 5HT3 receptors, and H1 receptor, is an effective antidepressant drug (32,33). It differs in structure and mechanism of action from other compounds of its class (32,33). Although mirtazapine alone is not used as an analgesic drug, its analgesic effects through opioid receptors and both serotonergic and noradrenergic receptors have been reported (34,35). Based on our results, low-dose pregabalin and mirtazapine were effective in the management of painful bone metastasis compared with twofold pregabalin. We thus believe that the present results showed the additive/synergistic effects of antiepileptic-antidepressant combination pharmacotherapy in the treatment of cancer-related neuropathic pain. Furthermore, mirtazapine has antiemetic effects as a 5HT antagonist (13,14), and as an H1 antagonist, it could stimulate appetite and increase body weight as well as regulate sleep disturbances (36). Although these beneficial secondary effects of mirtazapine were not evaluated in this study, the combination pharmacotherapy including mirtazapine might be an appropriate choice to treat cancer-induced bone pain in patients with many distressing somatic symptoms.

It is widely believed that the onset of beneficial antidepressant effects in depression is delayed for 2 or 3 weeks and maximal antidepressant-induced improvement of depression takes several weeks to occur (37).

Also, the pain-relieving effects of antidepressants are generally believed to occur about 2 weeks after the initiation of treatment (38). Referring to our previous results (12), however, the pain-reducing effects of antidepressants combined with antiepileptics occur in a week. Moreover, an interesting finding in the present study was that the pain-relieving effects of antidepressants in combination with antiepileptics appeared within a few days after the initiation of the treatment and remained for 2 weeks, compared with those of 2 antiepileptics. We thus postulate that the pain-reducing effects of antidepressants could appear faster under combination pharmacotherapy.

Although the combination pharmacotherapy is promising in treating cancer-induced bone pain, drug-drug interactions should be taken into consideration. Many drug-drug interactions are the result of an alteration of cytochrome P450 (CYP450) metabolism (39,40). Physicians should be cautious when prescribing a drug known to be metabolized by CYP450. The target drug may need to be substituted or the dose adjusted to account for a potential decrease or increase in metabolism. Among drugs used in this study, oxycodone, imipramine, and mirtazapine are predominantly metabolized by CYP2D6 (41). We think that the absence of significant drug-drug interactions in this study was possibly due to the low dose of each drug. Compared with tricyclic antidepressants including imipramine, mirtazapine as a newer antidepressant rarely inhibits CYP isoforms and is not expected to affect the disposition of concomitantly administered drugs (41). Therefore, in terms of the drug-drug interaction, the combination of mirtazapine and pregabalin in addition to opioids would be theoretically more favorable than the combination of imipramine and pregabalin. Further clinical studies are needed to prove this.

CONCLUSION

In conclusion, low-dose pregabalin-antidepressant combinations with opioids were effective in the management of painful bone metastases without severe adverse effects.

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