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Citation for published version:

Digital Object Identifier (DOI):
10.1200/JCO.2015.63.8221

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published in:
Journal of Clinical Oncology

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Randomized Double-Blind Trial of Pregabalin Versus Placebo in Conjunction With Palliative Radiotherapy for Cancer-Induced Bone Pain

Marie Fallon, Peter J. Hoskin, Lesley A. Colvin, Susan M. Fleetwood-Walker, Douglas Adamson, Anthony Byrne, Gordon D. Murray, and Barry J.A. Laird

See accompanying editorial on page 524

ABSTRACT

Purpose
Cancer-induced bone pain (CIBP) affects one third of patients with cancer. Radiotherapy remains the gold-standard treatment; however, laboratory and clinical work suggest that pregabalin may be useful in treating CIBP. The aim of this study was to examine pregabalin in patients with CIBP receiving radiotherapy.

Patients and Methods
A multicenter, double-blind randomized trial of pregabalin versus placebo was conducted. Eligible patients were age ≥ 18 years, had radiologically proven bone metastases, were scheduled to receive radiotherapy, and had pain scores ≥ 4 of 10 (on 0-to-10 numeric rating scale). Before radiotherapy, baseline assessments were completed, followed by random assignment. Doses of pregabalin and placebo were increased over 4 weeks. The primary end point was treatment response, defined as a reduction of ≥ 2 points in worst pain by week 4, accompanied by a stable or reduced opioid dose, compared with baseline. Secondary end points assessed average pain, interference of pain with activity, breakthrough pain, mood, quality of life, and adverse events.

Results
A total of 233 patients were randomly assigned: 117 to placebo and 116 to pregabalin. The most common cancers were prostate (n = 88; 38%), breast (n = 77; 33%), and lung (n = 42; 18%). In the pregabalin arm, 45 patients (38.8%) achieved the primary end point, compared with 47 (40.2%) in the placebo arm (adjusted odds ratio, 1.07; 95% CI, 0.63 to 1.81; P = .816). There were no statistically significant differences in average pain, pain interference, or quality of life between arms. There were differences in mood (P = .031) and breakthrough pain duration (P = .037) between arms. Outcomes were compared at 4 weeks.

Conclusion
Our findings do not support the role of pregabalin in patients with CIBP receiving radiotherapy. The role of pregabalin in CIBP with a clinical neuropathic pain component is unknown.

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INTRODUCTION

Cancer-induced bone pain (CIBP) is the most common type of cancer pain, affecting one third of patients.1,2 CIBP exists as a combination of background and breakthrough pain, with the latter either being related to events (eg, physical activity) or occurring spontaneously without any obvious precipitating factor.3 In CIBP, this poses a particular challenge. Standard analgesics (eg, opioids, nonsteroidal anti-inflammatory drugs, bisphosphonates) may be useful in controlling background pain; however, they are often ineffective in treating breakthrough pain.4

Radiotherapy is the gold-standard treatment for CIBP; however, meta-analyses have demonstrated that only 25% of patients will achieve complete pain relief, whereas 41% will achieve partial pain relief, with onset of analgesia taking 4 to 6 weeks.5 Many patients with CIBP do not achieve acceptable levels of analgesia.

Animal models have been developed to understand the pathophysiology of CIBP.6 Focal bone cancer pain models are used currently, and these provide a robust model (with features similar to
CIBP in humans). Through these, it has become evident that the underlying pathophysiology of CIBP differs from that in standard neuropathic or inflammatory pain models, although containing elements of both as well as involving additional factors arising from host–cancer cell interactions.7,8 Excitability in dorsal horn sensory processing pathways is markedly increased, resulting in both electrophysiologic and behavioral hypersensitivity. This means that painful and nonpainful peripheral nerve input (eg, touch, vibration, thermal stimuli) result in ongoing and stimulus-evoked pain that can be exacerbated by movement.

Animal models have been used to assess whether agents used for neuropathic pain could correct the abnormal dorsal horn neuronal architecture and minimize the central sensitization, which also exists in CIBP—particularly whether drugs that bind to the α2-δ subunit of calcium channels (eg, pregabalin, gabapentin) could act to reduce pain transmission. Expression of the α2-δ1 subunit in dorsal root ganglia is increased after peripheral nerve injury, where it is thought to facilitate channel trafficking to the plasma membrane and thereby contribute to development of central sensitization and pain hypersensitivity.9-12 Pregabalin and gabapentin have proven efficacy in a variety of chronic pain models (eg, nerve injury), probably through a reduction in excitatory neurotransmitter release and central sensitization.13 Animal studies have also reported efficacy in CIBP models, suggesting that pregabalin and gabapentin may be of value clinically in treating CIBP.9

In the clinical setting, pregabalin is being used increasingly to treat CIBP.14-17 This may be the result of emerging animal studies but may also be because of anecdotal findings. In palliative care, many of the drugs used in routine clinical practice have limited or no evidence supporting their use, but they are embedded in clinical practice. Therefore, it is fundamental that pregabalin be examined in a robust clinical trial within the relevant population before it becomes more widely adopted as a treatment for CIBP.

Following this translational paradigm, and given the need to improve management of CIBP and the need to assess the role of pregabalin fully in the clinical setting, a randomized double-blind trial of pregabalin (Lyrica; Pfizer, Tadworth, United Kingdom) versus placebo in conjunction with palliative radiotherapy for CIBP was conducted. Our hypothesis was that α2-δ calcium channel ligands may have a role in CIBP in humans, mirroring the preclinical findings.

**PATIENTS AND METHODS**

**Trial Design and Participants**

This was a multicenter, double-blind randomized trial of pregabalin versus placebo in conjunction with palliative radiotherapy for CIBP. Eligible patients were age ≥ 18 years, had radiologic evidence of metastatic bone disease, and were scheduled to receive radiotherapy for ≥ 1 site of clearly identifiable bone pain. Other key inclusion criteria were: life expectancy > 2 months, pain score (worst pain) ≥ 4 (on 0-to-10 numeric rating scale [NRS]) at the site of pain, scheduled to be treated with radiotherapy at that site, and ability to provide written informed consent. The main exclusion criteria were: current gabapentin or pregabalin use, significant renal impairment (creatinine clearance < 60 mL/min), and receiving wide-field irradiation. Patients who had any change in anticancer therapy before entering the trial with the potential to influence pain during the trial were excluded. Initially, radiotherapy to vertebral sites was an exclusion criterion, but this was subsequently removed as a major protocol modification, as discussed and approved by the trial steering committee, after 14 patients had been consented. The trial was conducted in five cancer centers in the United Kingdom: the Beatson West of Scotland Cancer Centre (Glasgow), Edinburgh Cancer Centre (Edinburgh), Velindre Cancer Centre (Cardiff), Princess Alexandra Tayside Cancer Centre (Dundee), and Mount Vernon Hospital (London).

**Procedures**

After giving consent, patients entered a run-in phase (maximum, 2 weeks) where their analgesia was optimized before radiotherapy to ensure, where possible, there were minimal changes in analgesia after random assignment and radiotherapy and to allow the effect of the intervention (pregabalin or placebo) alone to be assessed. In such cases,
patients would have stable pain; however, this would still be suboptimal, necessitating the need for radiotherapy.

Some patients had stable pain control and analgesic requirements before random assignment. Others had to have analgesics modified before random assignment. At the point of receiving radiotherapy, patients were only randomly assigned if they still met the eligibility criteria, with critically worst pain score ≥ 4 (0-to-10 NRS).

The radiotherapy regimen was either 8 Gy in one fraction or 20 Gy in five fractions, as per the decision of the patient's oncologist. Baseline assessments were performed in the 24 hours before the first fraction. Random assignment was carried out after the baseline assessments and before radiotherapy. Patients received either pregabalin or placebo and were given a 35-day supply of medication. Patients were instructed to take one capsule of the trial medication twice daily (12 hours apart). Each capsule contained either 75 mg of pregabalin or placebo. The trial medication was supplied free by Pfizer.

Patients were contacted every 2 to 3 days to encourage compliance with the medication and monitor for any adverse events. Every 7 days from baseline (days 8, 15, and 22), a formal assessment of analgesia was undertaken. Where a clinically meaningful improvement in pain had not occurred (defined as ≥ 2-point decrease on 0-to-10 NRS and/or patient felt adequate analgesia had not been achieved), the dose of the trial medication was increased as follows: baseline (day 1), pregabalin or placebo 75 mg twice daily; day 8, pregabalin or placebo 150 mg twice daily; day 15, pregabalin or placebo 225 mg twice daily; and day 22, pregabalin or placebo 300 mg twice daily.

**End Points**

End points were assessed at 1, 2, 3, and 4 weeks after the first fraction of radiotherapy. Analyses relate to assessments at 4 weeks unless otherwise stated.

The primary end point was improvement in CIBP at the site of radiotherapy by week 4. An improvement was a reduction of ≥ 2 points on a 0-to-10 NRS for worst pain, accompanied by a stable or reduced opioid points in clinical trials in bone metastases.18,19 Studies of analgesic interventions and is in keeping with guidelines on end radiotherapy by week 4. An improvement was a reduction of

**Statistical Analysis**

This analysis was based on the objective of showing superiority of pregabalin versus placebo in improving CIBP using the primary end point. An intention-to-treat approach was used.

The null hypothesis tested was that there was no difference in analgesia between the trial arms. A sample size of 206 patients was planned, based on the assumption that 50% of patients in the placebo arm would improve (ie, experience ≥ 2-point drop in worst pain score against background of stable or reduced opioid dose). To detect an improvement to 70% (ie, treatment effect of 20%) in the pregabalin arm, 103 patients were required to complete each arm, using a two-sided \( \chi^2 \) test with \( \alpha \) of 0.05% and 80% power.

**Results**

From August 13, 2008, to April 30, 2012, 233 patients were randomly assigned. The trial was stopped early (after 233 patients had been randomly assigned [target, \( n = 260 \)]) on the basis of slow recruitment, evidenced by the fact that only one in eight patients screened was consented, as seen in the CONSORT diagram (Fig 1). The main reasons patients were unable to participate were poor renal function (19.0%), patient declined (8.7%), concomitant use of pregabalin or gabapentin (6.9%), or insufficient pain (4.5%).
Patient demographics are listed in Table 1. One hundred twenty-seven patients (55%) were male, and the mean age (± standard deviation) was 65.5 (± 10.97) and 63.7 (± 11.25) years for the placebo and pregabalin arms, respectively. Prostate (n = 88; 38%), breast (n = 77; 33%), and lung (n = 42; 18%) were the most common cancer types. Baseline characteristics were similar between the groups.

In the pregabalin arm, 45 patients (38.8%) achieved the primary end point, compared with 47 (40.2%) in the placebo arm (adjusted odds ratio, 1.07; 95% CI, 0.63 to 1.81; P = .816). The observed absolute difference in response rates was 1.4% in favor of the placebo (40.2% v 38.8%), with a 95% CI ranging from 13.9% to 11.2% in favor of pregabalin. In the pregabalin group, 18 patients (15.5%) did not achieve the 2-point reduction in worst pain but remained on a stable or decreased opioid dose; 21 (18.1%) had an increase in opioid dose, and 32 (27.6%) could not be assessed (assumed nonresponse). In the placebo group, 14 patients (11.9%) did not achieve the 2-point reduction in worst pain but instead remained on a stable or decreased opioid dose; 31 (26.5%) had an increase in opioid dose, and 25 (21.4%) could not be assessed (assumed nonresponse).

Figure 2A details the worst pain from baseline to end point (week 4) per trial arm. The adjusted difference in mean worst pain scores between trial arms was 0.13 (95% CI, −1.02 to 0.75; P = .769). Figure 2B details the average pain from baseline to end point (week 4) per trial arm. The adjusted difference in mean average pain scores was 0.52 (95% CI, −1.22 to 0.19; P = .150).

Table 2 summarizes the BPI Intensity and Interference subscale, HADS, and EuroQol scores between trial arms. The adjusted mean difference between arms for BPI Intensity score was −0.7 (95% CI, −3.5 to 2.1; P = .606). The adjusted mean difference between trial arms for BPI Interference score was −1.8 (95% CI, −7.4 to 3.9; P = .537). There was no difference in HADS score between study arms (−1.1; 95% CI, −2.1 to 0.1; P = .031), but no difference in EuroQol score (P = .825).

Table 3 lists the serious and common adverse events (AEs) between trial arms. Fifty-one serious AEs were reported: 27 (53%) in the pregabalin arm and 24 (43%) in the placebo arm. Only one serious AE was thought to be related to pregabalin. The most common AE in the pregabalin arm was cognitive disturbance (32 events).

Table 4 lists breakthrough pain characteristics. These were similar between arms, with the exception of duration of breakthrough pain episodes, which was lower in the pregabalin arm (P = .037).

DISCUSSION

This large clinical trial does not demonstrate an analgesic benefit from pregabalin in patients with CIBP receiving radiotherapy. Individual pain measures were similar across both arms, and the consistency of neutral primary and secondary end points supports that the study was sufficiently powered to detect a difference. Despite the trial under-recruiting, the primary result comfortably
A case report examined gabapentin in CIBP and suggested possible\
would not be clinically meaningful.18,19
the power calculation, and indeed, the 95% CIs were compatible
excludes the 20% advantage to pregabalin, which was the basis of
the power calculation, and indeed, the 95% CIs were compatible
with the maximum CIs present and the established role of pregabalin for
treating anxiety.
The current findings will have considerable implications for
clinical practice, because pregabalin is being used increasingly in
the setting of CIBP. Although basic science work was encouraging,
with a possible therapeutic role for
a2-6 calcium channel ligands in
rodent models of CIBP, there had been limited clinical validation.9
A case report examined gabapentin in CIBP and suggested possible
benefit.14 It was followed by a randomized trial of pregabalin versus
placebo, which suggested potential value of pregabalin in CIBP, although
firm conclusions could not be drawn.15 Another study suggested pregabalin in combination with mirtazapine may be
beneficial; however, it advised additional trials.16 Nevertheless,
despite the limited evidence, pregabalin is often prescribed for
CIBP, with some reviews of CIBP management recommending the
use of pregabalin if there is a neuropathic component to the pain.17
However, our findings do not support a role for pregabalin in CIBP, and we suggest that its clinical role in CIBP be reconsidered.
The challenges of translating laboratory findings clinically, in
pain, include the difficulty in replicating multidimensional pain in
animals and the subjectivity of testing in laboratory conditions.23
In clinical trials of patients with peripheral neuropathic pain,
gabapentinoids have consistently demonstrated significant benefit.24-26 However, only a minority of patients achieved sub-
stantial pain relief, with many not responding. Patients with CIBP
generally have multiple serious morbidities and a more complex
array of factors contributing to their hypersensitivity, as a result of
immunologic responses to the cancer. Their pain state is more
complex and may be less readily reversible by pharmacologic
interventions. Animal models may also not respond to therapeutic
intervention either qualitatively or quantitatively in the same way
as patients with CIBP. These and other reasons may have resulted
in the lack of translation of our findings seen herein.
The trial had some limitations. All patients had metastatic
cancer, and as such, many had different sites of pain. We focused on
the area of pain corresponding to the radiotherapy site, and pain
assessments were performed accordingly. Also, patients’ overall
conditions were deteriorating, in keeping with the advanced nature
of their disease, and therefore, quality-of-life parameters could
have changed. The end point measures were assessed 4 weeks after
radiotherapy. It has been advocated that the optimal time for
assessing response to radiotherapy for CIBP is 8 weeks, and we
cannot be certain that additional differences would not have been
evident if the trial had assessed end points at this time.27 However,
although there may have been a greater number responding, the
relative difference between the two arms would not be expected to
change across a period from 4 to 8 weeks. The optimal dose of
pregabalin in this setting of advanced cancer is not known, and again,
it could be argued that higher doses or longer trial duration should
have been used. Patients were, however, titrated to the maximum-
tolerated dose, which resulted in 67% of patients achieving a dose of
≥ 300 mg daily for at least 3 weeks. These aspects have to be

| Table 2. BPI, EuroQol, and HADS Scores Between Treatment Arms |
|----------------|----------------|----------------|
| Measure       | Baseline       | End Point (week 4) |
|               | No. (% | Mean ± SD | Mean ± SD | Change | Difference | Adjusted Difference* |
| BPI Intensity | Pregabalin    | 115(51) | 18.6 ± 7.5 | 85(51) | 9.5 ± 9.1 | 8.3(51) | 10.5 | −0.4(51) | −3.3 to 2.4 | 0.762 | −0.7(51) | −3.5 to 2.1 | 0.606 |
|               | Placebo       | 114(51) | 18.7 ± 6.6 | 94(51) | 10.1 ± 7.7 | 8.7(51) | 8.6 | −1.4(51) | −7.0 to 4.2 | 0.629 | −1.8(51) | −7.4 to 3.9 | 0.537 |
| BPI Interference | Pregabalin    | 110(51) | 37.9 ± 16.3 | 80(51) | 24.2 ± 19.3 | 9.9(51) | 18.4 | −1.4(51) | −7.0 to 4.2 | 0.629 | −1.8(51) | −7.4 to 3.9 | 0.537 |
|               | Placebo       | 113(51) | 36.5 ± 14.5 | 90(51) | 26.0 ± 18.3 | 11.3(51) | 18.0 | −0.6(51) | −8.0 to 6.8 | 0.868 | −0.8(51) | −8.2 to 6.6 | 0.825 |
| EuroQol       | Pregabalin    | 114(51) | 54.6 ± 19.6 | 86(51) | 60.1 ± 24.1 | 3.8(51) | 24.1 | −1.0(51) | −2.0 to −0.1 | 0.039 | −1.1(51) | −2.1 to −0.1 | 0.031 |
|               | Placebo       | 113(51) | 55.3 ± 19.6 | 92(51) | 60.2 ± 23.0 | 4.4(51) | 25.5 | −1.0(51) | −2.0 to −0.1 | 0.039 | −1.1(51) | −2.1 to −0.1 | 0.031 |
| HADS          | Pregabalin    | 105(51) | 19.8 ± 3.3 | 82(51) | 20.8 ± 3.0 | −0.8(51) | 3.3 | −1.0(51) | −2.0 to −0.1 | 0.039 | −1.1(51) | −2.1 to −0.1 | 0.031 |
|               | Placebo       | 112(51) | 20.7 ± 3.0 | 88(51) | 20.5 ± 3.1 | 0.2(51) | 3.1 | −1.0(51) | −2.0 to −0.1 | 0.039 | −1.1(51) | −2.1 to −0.1 | 0.031 |

Abbreviations: BPI, Brief Pain Inventory; HADS, Hospital Anxiety and Depression Scale; SD, standard deviation.
*Adjusted for three randomization stratification factors: fractionation regimen, cancer type, and site of bone metastasis.

| Table 3. Adverse Events |
|------------------------|---------------------|
| Adverse Event          | No. (%               |
|                        | Pregabalin Arm | Placebo Arm |
| Serious                | 27(51)          | 24(47)       |
| Expected†              | 19(37)          | 11(22)       |
| Likely related to IMP† | 1(2)             | 2(4)         |
| Common                 | 183(67)         | 83(31)       |
| Nausea                 | 15(6)           | 21(8)        |
| Cognitive disturbance  | 23(9)           | 8(3)         |
| Vomiting               | 9(3)            | 8(3)         |
| Fatigue                | 11(4)           | 8(3)         |
| Pain                   | 8(3)            | 10(4)        |

Abbreviation: IMP, investigational medicinal product.
†In opinion of investigator.
‡Most common events.
considered in the context of high attrition, which may have increased further with longer trial duration. We also acknowledge that patients who have CIBP with neuropathic features may be more likely to benefit from pregabalin than those without; however, this was outside the scope of our trial. In our trial, we looked at those patients referred to radiation oncology for consideration of palliative radiotherapy for uncontrolled CIBP. Clearly, patients treated successfully with pregabalin or gabapentin, because of CIBP with clinical neuropathic features, would not have reached radiation oncology and therefore screening in this study. Undertaking pain trials in patients with cancer is challenging, but our trial succeeded by using a rigorous, well-designed protocol, a small number of centers, and focused patient follow-up.

Despite the neutral findings, we support the opinion of Hardy et al. on the need for trials in patients with advanced cancer. Currently, the majority of symptom control practice is based on either historical anecdote or low-level evidence, and the lack of research is paradoxical to its importance. There is a need for well-designed clinical trials that either support or (as in our trial) refute practice. We have demonstrated that undertaking symptom control trials in patients with cancer is feasible.

In conclusion, our findings do not support the role of pregabalin in patients receiving radiotherapy for CIBP. Future trials examining pregabalin in CIBP with a neuropathic pain component would be of interest.

Table 4. Breakthrough Pain

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pregabalin Arm (n = 45)</th>
<th>Placebo Arm (n = 54)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>30 (67)</td>
<td>30 (56)</td>
<td>.230</td>
</tr>
<tr>
<td>4-6</td>
<td>6 (13)</td>
<td>12 (22)</td>
<td></td>
</tr>
<tr>
<td>&gt; 7</td>
<td>8 (18)</td>
<td>6 (11)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
<td>6 (11)</td>
<td></td>
</tr>
<tr>
<td>Severity (0-10 NRS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>19 (46)</td>
<td>15 (29)</td>
<td>.175</td>
</tr>
<tr>
<td>4-6</td>
<td>10 (24)</td>
<td>16 (31)</td>
<td></td>
</tr>
<tr>
<td>&gt; 7</td>
<td>12 (29)</td>
<td>20 (39)</td>
<td></td>
</tr>
<tr>
<td>Duration of episode, minutes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>7 (21.88)</td>
<td>4 (8.51)</td>
<td>.037</td>
</tr>
<tr>
<td>1-15</td>
<td>17 (53.13)</td>
<td>19 (40.43)</td>
<td></td>
</tr>
<tr>
<td>16-30</td>
<td>5 (15.63)</td>
<td>12 (25.53)</td>
<td></td>
</tr>
<tr>
<td>31-60</td>
<td>1 (3.13)</td>
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<td></td>
</tr>
<tr>
<td>60-120</td>
<td>0 (0.00)</td>
<td>2 (4.26)</td>
<td></td>
</tr>
<tr>
<td>&gt; 120</td>
<td>2 (6.25)</td>
<td>5 (10.64)</td>
<td></td>
</tr>
<tr>
<td>Time from onset to maximum intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unpredictable</td>
<td>11 (34.38)</td>
<td>11 (22.92)</td>
<td>.123</td>
</tr>
<tr>
<td>&lt; 10 seconds</td>
<td>11 (34.38)</td>
<td>9 (18.75)</td>
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</tr>
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<td>10 seconds to 5 minutes</td>
<td>6 (18.75)</td>
<td>16 (33.33)</td>
<td></td>
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<tr>
<td>6-30 minutes</td>
<td>4 (12.50)</td>
<td>10 (20.83)</td>
<td></td>
</tr>
<tr>
<td>31-60 minutes</td>
<td>0 (0.00)</td>
<td>2 (4.17)</td>
<td></td>
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<tr>
<td>Predictability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>15 (39.47)</td>
<td>21 (41.18)</td>
<td>.657</td>
</tr>
<tr>
<td>Sometimes</td>
<td>15 (39.47)</td>
<td>16 (31.37)</td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td>0 (0.00)</td>
<td>3 (5.88)</td>
<td></td>
</tr>
<tr>
<td>Almost always</td>
<td>2 (5.26)</td>
<td>7 (13.73)</td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>6 (15.79)</td>
<td>4 (7.84)</td>
<td></td>
</tr>
<tr>
<td>Use of analgesia</td>
<td></td>
<td></td>
<td>.266</td>
</tr>
<tr>
<td>Every time</td>
<td>8 (21.05)</td>
<td>8 (16.00)</td>
<td></td>
</tr>
<tr>
<td>Most of the time</td>
<td>9 (23.68)</td>
<td>13 (26.00)</td>
<td></td>
</tr>
<tr>
<td>Some of the time</td>
<td>6 (15.79)</td>
<td>16 (32.00)</td>
<td></td>
</tr>
<tr>
<td>Hardly ever</td>
<td>9 (23.68)</td>
<td>6 (12.00)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>6 (15.79)</td>
<td>7 (14.00)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NRS, numeric rating scale.
*Mann-Whitney test.

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Data analysis and interpretation: Marie Fallon, Susan M. Fleetwood-Walker, Gordon D. Murray, Barry J.A. Laird
Manuscript writing: All authors
Final approval of manuscript: All authors

Disclosures provided by the authors are available with this article at www.jco.org.
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Speakers’ Bureau: Mundipharma
Research Funding: Pfizer (Inst), Astellas Pharma (Inst), Mundipharma (Inst)

Peter J. Hoskin
Research Funding: Varian Medical Systems (Inst), Astellas Pharma (Inst), Bayer (Inst)

Lesley A. Colvin
No relationship to disclose

Susan M. Fleetwood-Walker
No relationship to disclose

Douglas Adamson
Stock or Other Ownership: GlaxoSmithKline (I)
Research Funding: Roche (Inst)

Anthony Byrne
Speakers’ Bureau: Actavis

Gordon D. Murray
Consulting or Advisory Role: Servier

Barry J.A. Laird
Speakers’ Bureau: Pfizer

Research Funding: Pfizer (Inst)
Acknowledgment

We thank all the nursing staff who assisted in the study, particularly Dorothy Boyle and Anne Todd, and the Edinburgh Clinical Trials Unit.