Pain response and quality of life assessment in patients with moderate/severe neuropathic pain due to bone metastasis undergoing treatment with palliative radiotherapy and tapentadol: A prospective multicentre pilot study

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Abstract

Introduction: To assess pain response rate (RR) and quality of life (QoL), in patients with moderate/severe neuropathic pain (NP) due to bone metastasis (BM) undergoing palliative 3D radiotherapy plus tapentadol.

Methods: We conducted a prospective multicentre pilot study. Patients were assessed before radiotherapy using the validated questionnaire (Douleur Neuropathique en 4 questions). Response to radiotherapy (8 Gy–30 Gy/1–10 fr) at one and two months was assessed according the International Bone Metastases Consensus criteria. Inclusion criteria: radiological evidence of BM, NP according to DN4 (cut-off score ≥4), no spinal cord compression, worst pain score ≥5/10. Nonparametric Mann–Whitney U test compared changes in QoL among response groups.

Results: Seventeen patients (13 men, 4 woman), median age 67 years (42–81), were included. Pre-treatment median pain severity was 7.5 (5–10). Median dose of tapentadol administered before radiotherapy was 100 mg/24 h (100–300 mg). Overall RR 1 month after radiotherapy was 10/16 = 62.5%: 3/16 (18.8%) achieving a complete response (CR) and 7/16 (43.8%) a partial response (PR). Overall RR 2 months after RT was 5/10 (50%): 10% a CR and 40% a PR. ITT RR for this study at 1 and 2 months was 10/17 = 59% and 5/17 = 29%, respectively. Patients responding to radiotherapy had significant improvement in EORTC QLQ-C30 emotional functioning (EF) (p = 0.025) and fatigue symptom scale scores (p = 0.035) one month after radiotherapy. Painful site symptom QLQ-BM22 scores improved 2 months after radiotherapy (p = 0.024).

Conclusions: Palliative radiotherapy plus tapentadol shows an acceptable pain response and QoL improvement especially regarding EF, fatigue and painful site symptom scales in patients with moderate/severe NP due to BM. Therefore, it could be an alternative to manage NP in daily practice.

Key words: bone metastasis; pain; neuropathic pain.
Introduction

Treatment of pain due to bone metastasis constitutes a significant proportion of the workload of radiotherapy (RT) departments, approximately 20% of treatments overall. RT has been shown to be an effective palliative treatment for relieving metastatic bone pain and improving quality of life (QoL). Numerous randomized trials over the last two decades, including recent meta-analyses, have shown intention-to-treat overall response rates (RRs) of approximately 60% (with almost a third of patients achieving a complete response [CR]) and no significant difference (P = 0.18) in complete and overall pain relief between single and multifraction palliative RT for bone metastases. On the other hand, these trials have excluded patients with neuropathic bone pain (NBP) or have not identified patients with bone pain with a neuropathic component, allowing them to be distinguished from patients with uncomplicated (local) bone pain.

It is likely that NBP is underdiagnosed by radiation oncologists for various reasons. Patients sometimes have difficulty describing the symptoms. Additionally, not all clinicians have a good working knowledge of dermatomal sensory changes (hypo- or hyperaesthesia) or the pain may be confused with other bone metastases in a similar anatomical distribution. As a result, data on the proportion of patients with bone metastases who develop neuropathic pain are scarce. An exception are those from a prospective cross-sectional survey conducted by Kerba et al. indicating that approximately 20% of patients with bone metastases manifest bone pain with distinguishable neuropathic features and that these patients experience greater pain intensity (as assessed using a pain score) than those without neuropathic features.

Neuropathic pain is a poorly understood source of distress in cancer patients with bone metastasis and may be highly prevalent in RT oncology units. Indeed, it is notoriously resistant to pharmacological intervention. Tapentadol is an atypical opioid with a dual mechanism of action (as both an opioid agonist and noradrenalin reuptake inhibitor) and therefore is expected to be more effective in treating NBP than other opioids. To date, however, there is a lack of established clinical evidence for its use in cancer-related NBP.

On the other hand, only one randomized trial has explored the role of RT for NBP. In 1996, the Trans-Tasman Radiation Oncology Group (TROG) conducted a multicentre randomized study comparing a single 8 Gy fraction with 20 Gy in 5 fractions for neuropathic bone pain (TROG 96.05). They were associated with similar outcomes for NBP, although a single 8 Gy fraction was not found to be as effective as fractionated treatment (20 Gy in five fractions), with overall RRs (intention-to-treat RRs) of 53% and 61%, respectively.

According to Lechner et al., more frequent prescription of pain medications targeting neuropathic pain may be warranted in this patient population; however, no studies have assessed the utility of specific medication targeting NBP together with palliative RT. Therefore, the aim of our pilot study was to assess pain RRs and QoL in patients with moderate-to-severe NBP due to bone metastasis with a novel treatment approach based on tapentadol combined with palliative RT.

Methods

Study design

We conducted a prospective multicentre (three-hospital) pilot study of consecutive patients undergoing palliative RT for painful bone metastasis between December 2014 and November 2017. The study population comprised patients with known malignancy and bone metastasis causing neuropathic pain. The primary outcomes were treatment response and QoL assessment after palliative RT in patients receiving tapentadol retard as baseline painkiller for NBP.

The study was approved by the ethics committees of all three hospitals that participated in the study and has been conducted in accordance with the principles of the Declaration of Helsinki.

Eligibility criteria

The selection criteria were taken from the most recent international consensus on the evaluation of patients with bone metastases published in 2012 and were as follows.

Inclusion criteria: a diagnosis of cancer (confirmed histologically) and a life expectancy of ≥ 3 months, radiologically confirmed bone metastases that cause pain, pain score ≥ 5 (based on worst pain in the area to be treated in the previous 3 days on a scale of 0 to 10) and clinical picture compatible with neuropathic pain scoring ≥ 4 (on a scale of 0 to 10) on the Douleur Neuropathique Questionnaire (DN4). Additionally, the patient was required to be able to complete the data collection form and give written informed consent to participate.

Exclusion criteria: spinal cord or cauda equina compression in the area to be treated, a history of RT in the region of the current pain, medical contraindications to tapentadol retard, a baseline dose of morphine of over 160 mg/24 h that would require an equivalent dose of tapentadol retard- 500 mg/24 h, bone metastases in the region where the patient reported neuropathic pain (e.g. bone metastasis in the femur in a patient describing L2-L3 neuropathic pain) or neuropathic pain attributable to non-bone metastasis (brachial plexus or sacral invasion).

Treatment

All the patients received three-dimensional conformal radiation therapy. First, they all underwent a planning CT
scan, the treatment area (gross tumour volume) being delineated by ‘macroscopic’ radiological imaging and a margin of 1–2 cm added (planning target volume). In the case of vertebral lesions, the vertebra involved and the immediately neighbouring vertebrae were generally included. Since there is no standard radiation therapy regimen for neuropathic bone pain,13 the dose prescribed could be a single dose of 8 Gy or a fractionated dose of 20 Gy (4–5 fractions) or 30 Gy (10 fractions) at the discretion of the doctor in charge.

Regarding the pharmacological treatment, we administered tapentadol retard at an initial dose of 50 mg/12 h titrated up to a maximum of 500 mg/day (following the standard indications mentioned in the prescribing information for the drug). As well as the baseline medication with tapentadol, patients received rescue medication for breakthrough pain (if needed), following the algorithm proposed by Davies et al.15 at the discretion of the doctor in charge.

Any changes in the systemic treatment (chemotherapy or hormone therapy) or bisphosphonates within the 4 weeks prior to patient inclusion were recorded (Table 1). Treatment-associated toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE vs 4.0).

### Assessment

At baseline, and at 1 and 2 months after treatment, all patients underwent a physical examination, and data were collected on the pain medications used. The total daily dose (including rescue medication administered) was converted to an oral morphine-equivalent dose (OMED), and this was used to assess pain response category in line with international consensus recommendations on the evaluation of response to RT.16

The overall RR was defined as the sum of complete response (CR) and partial response (PR). In brief, in accordance with the international consensus,16 CR was defined as a pain score of 0 with no increase in analgesic intake whereas PR was defined as pain score reduction of ≥ 2 points without analgesic increase or analgesic reduction of ≥ 25% without an increase in pain score at the treated site. Pain progression is defined as an increase in pain score of 2 or more points with a stable OMED or a ≥ 25% increase in OMED from baseline with a pain score that is stable or 1 point above baseline, and an indeterminate response covers any cases that do not meet the criteria for a complete response, partial response or pain progression.

QoL was assessed at baseline, and 1 and 2 months after RT using the EORTC QLQ-C30 and bone metastasis-specific module BM22.

### Statistical analysis

The study duration was initially planned to be 2 years, in order to include 40 patients. Due to slow accrual, the study period was additionally extended (1 year) and finally closed without reaching the expected recruitment.

Descriptive statistics were calculated, using mean, median and standard deviation for continuous values, and counts and proportions for categorical values. Chi-squared, t-tests and Fisher’s exact tests were used to compare pain response at baseline with that at 1 and 2 months after treatment. The Wilcoxon nonparametric test was used to compare QoL baseline scores and QoL changes after treatment.

The change from baseline in QoL score at 1 month and 2 months after RT was calculated such that a positive difference indicated an improvement in quality of life. That is, for the functional scales, we calculated the following: follow-up score (at 1 or 2 months after RT) – baseline score (for each functional variable), a higher value indicating functional improvement; and for the symptom domains: baseline score (at 1 or 2 months after RT) – follow-up score (for each symptom variable), a higher value indicating improvement in symptoms.

First, QoL improvement after RT was assessed for the whole population and thereafter the QoL results were explored by treatment response (comparing changes in

### Table 1. Patient and treatment characteristics

| Variable | Count (Percentage) |
|----------|--------------------|
| Sex, men:women | 13 (76.5%): 4 (23.5%) |
| Age, years | Median 67 (range 42–81) |
| Baseline Karnofsky performance status | |
| ≥80% | 9 (53%) |
| ≤70% | 8 (47%) |
| Primary site | |
| Lung | 8 (47.1%) |
| Prostate | 2 (11.8%) |
| Kidney | 1 (5.9%) |
| Bladder | 2 (11.8%) |
| Thyroid | 1 (5.9%) |
| Head and neck | 1 (5.9%) |
| Colorectal | 1 (5.9%) |
| Hepatocarcinoma | 1 (5.9%) |
| Pain, index site | |
| Spine | 8 (47.1%) |
| Pelvis | 6 (35.3%) |
| Other | 3 (17.6%) |
| Pain characteristics | |
| Mixed/somatic and neuropathic | 15 (88.2%) |
| Only neuropathic | 2 (11.3%) |
| Pre-treatment pain severity at index site | |
| Median 7.5 (5–10) |
| Radiotherapy (3D conformal) | |
| 8 Gy (one fraction) | 2 (11.8%) |
| 20 Gy, 4-5 fractions | 10 (58.8%) |
| 30 Gy, 10 fractions | 5 (29.4%) |
| Chemotherapy in the 4 weeks | |
| No 11 (64.7%) before palliative RT | Yes 6 (35.3%) |
| Foci of metastasis other than bone | |
| No 8 (47.1%) | Yes 9 (52.9%) |
| Bisphosphonates in the 4 weeks | |
| No 12 (70.6%) before palliative RT | Yes 5 (29.4%) |

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QoL in responders and non-responders to RT using the nonparametric Mann–Whitney U test).

For all statistical tests, P values less than 0.05 were considered to indicate significance. All statistical analyses were conducted using IBM SPSS for Windows v22 (IBM Corp, Armonk, NY, USA).

Results

A total of 17 patients were included, 13 men and 4 women, and their median age was 67 years (42–81). Patient and treatment characteristics are summarized in Table 1.

The median baseline pain score (for worst pain in the last 72 h) was 7.5 (range 5–10). Regarding pain characteristics, 15 patients had mixed pain (with somatic and neuropathic components) while 2 patients only had neuropathic pain. At baseline, 10/17 (58.8%) patients presented breakthrough pain according to the Davies algorithm.15

Painkillers taken at baseline, as recorded in the first clinical visit, were opioids in 15 patients (transdermal fentanyl in three, tramadol in six, oral morphine in two and oxycodone in three cases) and only non-opioids in two patients. Further, in addition to baseline opioids, non-steroidal anti-inflammatory drugs were used by four patients, corticosteroids by two patients and both at the same time by three patients. Use of adjuvant analgesics such as gabapentin, duloxetine and pregabalin at baseline was recorded in four patients.

The patient-reported reason for changing the baseline opioid medication and starting tapentadol was as follows: lack of efficacy in 16/17 (94%) and adverse effects in 1/17 (6%). The median dose of tapentadol administered before RT was 100 mg/24 h (100–300 mg). Four patients stopped tapentadol during the study (1 due to grade III constipation, 1 due to grade II dizziness, 1 due to grade II diarrhoea and 1 for unknown reasons).

The median time between baseline assessment and starting RT (first session) was 6 days (range 1–13). Regarding pain response (numeric rating scale; 0–10), patients obtained a median pain score of 7.5 (5–10) at baseline, and lower median scores of 3 (0–10) (P = 0.006) and 5 (0–9) (P = 0.037) at 1 and 2 months after treatment, respectively.

Sixteen patients were assessable 1 month after the end of RT and 10 at 2 months. At 1 month, the overall RR was 10/16 (62.5%), with a CR in 3/16 (18.8%) and a PR in 7/16 (43.8%), while three patients (18.8%) showed pain progression and three patients (18.8%) an indeterminate response. At 2 months after RT, the overall RR was 50% (5/10), one patient (10%) achieving a CR and the others (40%) a PR. At this point, two patients (20%) showed pain progression and three (30%) an indeterminate response. It should be noted that the ITT RR for this study at 1 and 2 months was 10/17 = 59% and 5/17 = 29%, respectively.

We also evaluated the response specifically in relation to neuropathic pain, comparing DN4 scores at 1 and 2 months after RT with those at baseline. To summarize the results, we calculated the percentage of patients that had a DN4 score ≥ 4, suggesting that neuropathic pain was not detectable, and this was considered a favourable response in terms of the neuropathic pain component. One month after RT, only 3 out of the 16 assessable patients had a DN4 score ≥ 4, the others (13/16 patients, 81.2%) experiencing a favourable response in terms of neuropathic pain, the reduction in pain score being statistically significant (P < 0.001). On the other hand, 2 months after RT only 3 out of 10 assessable patients had a DN4 score ≥ 4, meaning that 7/10 patients (70%) experienced a favourable response of the neuropathic pain component, and again the reduction in pain score was statistically significant (P < 0.016).

Overall, for EORTC QLQ-C30, the median global health scores at baseline vs 1 month and baseline vs 2 months after RT were as follows: 33.33 (0–66.67) vs 50 (25–83.33) (p = 0.013) and 33.33 (16.67–66.67) vs 75 (33.33–91.67) (P = 0.011), respectively. See Figure 1.

One month after RT, patients who responded showed significant improvement in EORTC QLQ-C30 emotional functioning (responders: 18 [−41.67 to 58.33] vs non-responders: −12.5 [−33.33 to 8.33], P = 0.025) and fatigue (responders: 16.6 [−55.56 to 44.44] vs non-responders: −11.1 [−11.11 to 22.22], P = 0.035). See Figures S1 and S2 and Table 2.

In patients who responded to RT, there was a significant difference in QLQ-BM22 painful site score between baseline and the 2-month follow-up (responders: 33.3 [33.33 to 46.67] vs. non-responders: 6.6 [−20 to 26.67], P = 0.024). See Figure S3.

There were no significant differences in other domains of the EORTC QLQ-C30 or QLQ-BM22. We note, however, that we observed a trend to improvement 1 month after RT in median scores on other functional scales; for example, for cognitive functioning responders scored 0 (−33.33 to 50) and non-responders −25 (−33.33 to 16.67), but the difference was not significant (P = 0.051) (Figure S4 and Table 2). Full data comparing QoL changes at 1 and 2 months after RT (follow-up score at 1 or 2 months – baseline score) are presented in Tables 2 and Table S1.

Regarding toxicity due to RT, 15 patients showed no signs of toxicity while 2 developed grade II enteritis.

Discussion

Our results indicate a good clinical response to tapentadol and palliative RT for managing moderate-to-severe neuropathic pain attributable to bone metastasis and that this approach is associated with an improvement in QoL.

The overall pain response at 1 month after completion of RT was 62.5%. The rate of overall response is within the range observed in other randomized studies.1,5,7,8.
The responses (intention-to-treat RRs) within 2 months obtained in the only randomized study we have found assessing the response to radiation in patients with neuropathic bone pain associated with bone metastasis were 53% for 8 Gy/1 fraction and 61% for 20 Gy/5 fractions, respectively. In addition, it should be emphasized that the ITT RR in our study at 1 and 2 months was $\frac{10}{17} = 59\%$ and $\frac{5}{17} = 29\%$, respectively.

It should be noted that the RRs reported in our study at 1 and 2 months are for assessable patients and therefore are not directly comparable to the quoted overall RRs for TROG 96.05 (and using different pain scores and response definitions). However, the overall RRs for assessable patients from TROG 96.05 were 61% for 8Gy/1 fraction and 72% for 20 Gy/5 fractions (compared with 62.5% at 1 month and 50% at 2 months for the whole cohort in the present study). Finally, the rates of CR of 18.8% at 1 month and 10% at 2 months after RT are lower than those reported for neuropathic pain by Roos et al. In the present study, all patients presented moderate-to-severe pain. Interestingly, 80% of the patients

| Table 2. Comparison of changes in median QOL scores among patients who responded differently to palliative radiation therapy 1 month after radiotherapy |
|---------------------------------------------------------------|
| **Responders (complete and partial response)** | **Non-responders** | **P value** |
| QLQ-BM22 scale | | |
| Painful sites | 20 (–20 to 46) | 6.6 (–20 to 20) | 0.188 |
| Pain characteristics | 33,3 (0 to 55.56) | 16.6 (–44.44 to 55.55) | 0.592 |
| Functional interference | 25 (19.7 to –20,83) | 2 (–37.50 to 37.5) | 0.175 |
| Psychosocial aspects | 0 (–22,22 to 50) | –10.5 (–55.56 to 5.56) | 0.174 |
| QLQ-C30 scale | | |
| Physical functioning | 10 (–53,33 to 33.33) | –13.3 (–33.33 to 26.67) | 0.299 |
| Role functioning | 0 (–50 to 66.67) | 0 (–66.67 to 16.67) | 0.955 |
| Emotional functioning | 18 (–41.67 to 58.33) | –12.5 (–33.33 to 8.33) | 0.025 |
| Cognitive functioning | 0 (–33.33 to 50) | –25 (–33.33 to 16.67) | 0.051 |
| Social functioning | 0 (–66.67 to 33.33) | –16.6 (–33.33 to 16.67) | 0.692 |
| Global health status | 20.8 (–8.33 to 50) | 8.3 (–25 to 50) | 0.413 |
| Fatigue | 16.6 (–55.56 to 44.44) | –11.1 (–11.11 to 22.22) | 0.035 |
| Nausea/vomiting | 0 (–33.33 to 33.33) | 0 (–83.33 to 0) | 0.118 |
| Pain | 33.3 (–33.33 to 66.67) | 33.3 (–66.67 to 100) | 0.737 |
| Dyspnoea | 0 (–33.33 to 33.33) | 0 (–33.33 to 33.33) | 0.628 |
| Insomnia | 33.3 (–33.33 to 100) | 33.3 (–66.67 to 100) | 0.737 |
| Appetite loss | 0 (–66.67 to 66.67) | 0 (0 to 33.33) | 0.491 |
| Constipation | 0 (–66.67 to 100) | 0 (0 to 33.33) | 0.719 |
| Diarrhoea | 0 (–33.33 to 33.33) | 0 (–33.33 to 0) | 0.572 |
| Financial problems | 0 (–33.33 to 33.33) | 0 (0 to 0) | 0.0 |

Bold indicates the results that are statistically significant.
included in TROG 96.05 (80%) also reported moderate or severe pain at enrolment.

The assessment of QoL in relation to pain response is a key factor in treatment. In general, studies assessing the management of pain due to bone metastases have not included an assessment of the impact of the pain response on QoL. Further, to our knowledge, our study is the first to assess QoL after RT specifically in patients with neuropathic pain. According to this pilot study, patients who responded to the RT showed a significant improvement in QoL on the pain symptoms scale, less fatigue and an improvement in emotional function according to the EORTC QLQ-C30 and specific module BM22. Other authors have shown similar results in patients with bone metastasis. Despite the small sample size in this study, results from the QLQ-BM22 specific module were able to identify statistically significant differences in QoL in the pain domain, highlighting its sensitivity. This shows the importance of using a specific QoL instrument (BM22) in patients with bone metastasis. Further, we found changes by 10 points or more (which could be interpreted as clinically relevant) indicating improvement in other aspects of QoL such as functional interference and overall health status (Table 2 and Table S1), though the results were not statistically significant, probably due to the small sample size.

Given the lack of an established optimal strategy for the treatment of neuropathic pain, we have investigated a new approach using tapentadol and RT and, to our knowledge, no previous studies have assessed this combined treatment specifically focused on the management of neuropathic pain. Tapentadol is a recent opioid. It has been used for chronic musculoskeletal pain and for the relief of cancer pain in adults. The efficacy of tapentadol is stated to be comparable to morphine and oxycodone and has been associated with a more favourable safety profile than oxycodone. Tapentadol is centrally acting analgesic medicine with a dual mechanism: acting at the G-opioid receptor and inhibiting noradrenaline reuptake. Therefore, it is expected to be better to treat neuropathic pain than other opioids and has been tested with this purpose in the present study. The rationale for combining tapentadol with RT for neuropathic bone pain was first to use an opioid with a modulatory effect on this type of pain, rather than other more commonly used opioids, such as fentanyl and morphine. In fact, one of the conditions for the inclusion of patients in this study was the lack of effectiveness of the analgesic medication given before attending the radiation oncology unit. Secondly, we assessed a cohort of patients on the same baseline medication (based on tapentadol), to facilitate the interpretation of the pain response to RT and changes in the neuropathic component of pain. It should also be emphasized that four patients ceased tapentadol during the study: three cases due to toxicity (1 due to grade III constipation, 1 due to grade II dizziness, 1 due to grade II diarrhoea) and 1 for unknown reasons (one patient stopped the medication without reporting any specific reason or adverse effect).

On the other hand, we recognize that this study has some limitations, in particular, its small sample size. Nonetheless, though there were few patients, the study population was selected using strict criteria, following the latest international guidelines, and even with this size of sample we have detected significant improvements in certain QoL items in responders (Table 2 and Table S1), as well as a good tolerance to the pharmacological treatment in patients with severe pain (baseline median of 7.5/10), that is patients with pain that is difficult to control.

Finally, we should highlight that in this study, we specifically assessed the characteristics of the pain before treatment, 15 patients showing pain with mixed characteristics (nociceptive and neuropathic) and two only neuropathic pain (Table 1). In the 17 patients with neuropathic pain at baseline, according to the DN4 criteria, the neuropathic pain component disappeared at 1 month after RT in 13 out of 16 patients (81.2%) and 7 out of 10 (70%) continued to report no neuropathic pain at 2 months. In this context, this is the first study with these characteristics showing a specific improvement in the neuropathic component of pain as well as in the 0/10-point numeric pain rating scale.

In conclusion, Palliative RT plus tapentadol produces an acceptable pain response and QoL improvement, in particular, in emotional functioning, fatigue and painful site scores, in patients with bone metastasis and moderate-to-severe NBP.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

**Table S1.** Comparison of changes in median QOL scores among patients who responded differently to palliative radiation therapy 2 months after radiotherapy.

**Fig. S1.** Improvement in EORTC QLQ-c30 emotional functioning in patients who responded to radiotherapy.

**Fig. S2.** Improvement in EORTC QLQ-c30 fatigue symptom in patients who responded to radiotherapy (one month after radiotherapy).

**Fig. S3.** Difference in EORTC QLQ-BM22 painful sites score between baseline and the 2-month follow-up.

**Fig. S4.** Improvement in EORTC QLQ-c30 cognitive functioning in patients who responded to radiotherapy (one month after radiotherapy).